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HAVERHILL FEVER

REPORT OF A CASE WITH REVIEW OF THE LITERATURE

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BROOKLYN

Haverhill fever is characterized by "an abrupt onset a rubella-form to morbilliform eruption chiefly on the extremities and an inflammation of the joints with marked pain and tenderness"¹ The diagnosis is made by isolation, from blood or from joint fluid, of a highly pleomorphic filamentous or spindle-shaped aerobic or microaerophilic gram-negative organism, *Haverhillia multiformis*,² which requires serum for growth in artificial mediums Recently, in the medical service of the Long Island College Hospital, a patient was observed who presented the clinical picture of Haverhill fever *Haverhillia multiformis* was isolated from the blood stream on seven occasions

REPORT OF CASE

A S, a 40 year old Italian woman, was admitted to the medical service of the Long Island College Hospital on Nov 19, 1937, complaining of pain and swelling of the joints of about five days' duration

She stated that three weeks before admission she had been bitten on the web between the fourth and the fifth finger of the left hand by a young rat encountered in the kitchen garbage receptacle The wound bled at the time The patient washed the hand and applied iodine to the bleeding area Complete healing followed, and the history of this trauma was not elicited until nearly a month after admission

About one week before the patient's entry a slight cough and a sore throat developed A sharp chill occurred, lasting about fifteen minutes That evening the patient felt feverish and had pain in both knees and both ankles For the

From the Department of Medicine and the Department of Bacteriology, the Long Island College of Medicine

1 Place, E H, and Sutton, L E Erythema Arthriticum Epidemicum (Haverhill Fever), Arch Int Med 54 659 (Nov) 1934

2 Parker, F, Jr, and Hudson, N P The Etiology of Haverhill Fever (Erythema Arthriticum Epidemicum), Am J Path 2 357, 1926

next four days she was confined to bed with headache, repeated vomiting and pain in the neck and back. A rash appeared around the knees and ankles.

Two days before admission the woman's condition improved sufficiently for her to get up, but a return of symptoms soon forced her again to bed. There now developed pain and swelling in the right shoulder, elbow and wrist. There was an increase in the pain and swelling of the knees and ankles.

Ten years before admission the patient had had pains of the joints with slight fever but was not confined to bed. Her general health otherwise had been good.

On physical examination the temperature was 103 F, the pulse rate 128, the respiratory rate 28 and the blood pressure 110 systolic and 70 diastolic. The woman seemed acutely ill. The throat was injected. The left lobe of the thyroid was slightly enlarged. The heart showed no murmurs, but there was some roughening of the first sound at the apex, and the second pulmonary sound was accentuated at the base. The abdomen was moderately tender in the right upper quadrant. The spleen was not felt. The neck showed pain on flexion. The right elbow and wrist were swollen, tender and painful when moved. The left wrist was tender but not swollen. Both knees were swollen and painful on movement, the right more than the left. Fluid was present in the right knee. The muscles of the back were tender. A maculopapular eruption was present on the extensor aspects of the lower parts of the legs. The diagnosis on admission was acute rheumatic fever.

The hemoglobin content of the blood was 70 per cent (Sahli), red cells numbered 4,190,000 and white cells 11,450, with 87 per cent polymorphonuclears. The sedimentation time was thirty-seven minutes (18 mm). The urine contained no albumin or casts. The blood contained 130 mg of sugar and 8 mg of urea nitrogen per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood were negative.

A roentgenogram of the chest taken on November 22 showed no evidence of active tuberculosis, but there was increase in interstitial fibrosis and evidence of fibrous pleuritis on the right.

Course in the Hospital—As shown in the chart (fig 1), the patient's temperature during the first week in the hospital (second week of the disease) fluctuated between 99.4 and 104.6 F before assuming a continuous level of about 100 F. Except for irregular elevation above that point during the third and fourth weeks in the hospital (fourth and fifth weeks of the disease), there was a gradual decline to a normal level over a total febrile period of about eight weeks.

The arthritis present on the patient's admission slowly subsided until December 22, when there was a return of pain in the right knee and left shoulder. This exacerbation lasted about four weeks, efforts at relief of pain were largely ineffectual, as in the first attack. Pain on motion, tenderness and swelling characterized the arthritic manifestations. Fluid was thought to be present only once in the right knee joint on the patient's admission. The fluid was not aspirated. At various times roentgen study of the right elbow, both shoulders, the lumbar portion of the spine, the sacroiliac joints and the hip joints gave negative results.

The eruption seemed to be of embolic rather than allergic type. It was maculopapular and was confined to the extremities. New lesions appeared from time to time during the illness, and some of these were frankly petechial, being red and tender at first, with a central pinpoint of hemorrhage. Several such lesions appeared on the fingers. The cutaneous lesions never suppurated but subsided slowly, leaving pigmented areas which later underwent desquamation.

During this illness the patient's general condition remained surprisingly good. Apart from the pain and discomfort of the arthritis, she suffered little incon-

venience from the fever or other accompaniments of the infection. It was found that with exercise the typical signs of mitral stenosis could be elicited. It was felt that the woman had an old rheumatic lesion referable to her earlier attacks of arthritis.

Treatment included the administration of salicylates, which was largely ineffective, and of codeine, which gave fairly good results. During a period of six days, from December 11 through December 16, a total of 127 Gm of sulfanilamide was given without apparent influence on the course of the infection. Because of its reported efficacy in actinomycosis,³ administration of 1 Gm of thymol daily was started on Jan 17, 1938, and continued with brief intermissions for about three

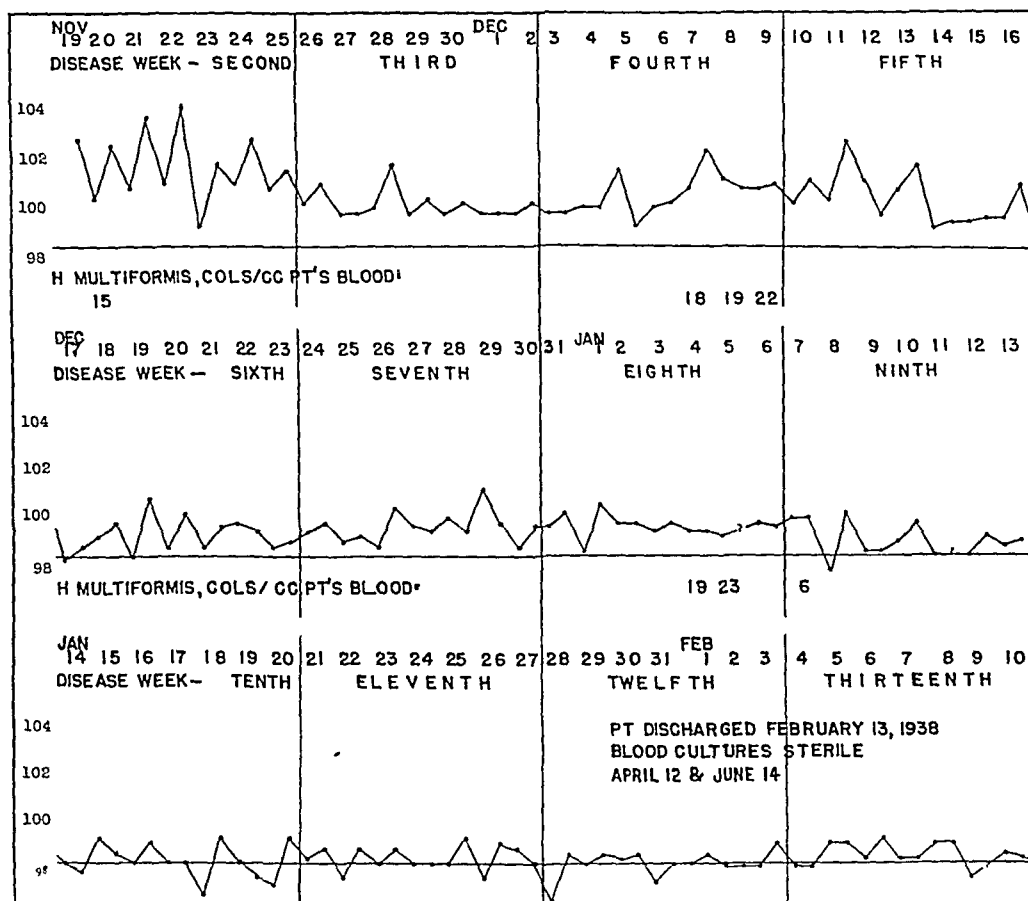


Fig 1—Chart of temperature (F) in a case of Haverhill fever. Only readings taken at 8 a m and 8 p m are shown.

weeks. After introduction of this drug the fever remained below 100 F, but the medication was begun late in the course of the disease, and the clinical impression was that it probably had no specific action.

Course After Leaving the Hospital—The patient was discharged from the hospital on February 13, having been completely afebrile for about two weeks. There was still some disability in the left shoulder, but the other joints were apparently normal in appearance and in function. After a period of relative freedom from symptoms, pain recurred in the left shoulder and to a lesser extent in

3 Myers, H B. Thymol Therapy in Actinomycosis, J A M A 108 1875 (May 29) 1937

the left elbow This was noted during May During the latter part of June diathermy was used with apparent success At the time of writing there has been no recurrence of the acute arthritic symptoms, other than that just noted, nor has there been a return of the cutaneous lesions which were present on the patient's admission to the hospital

Bacteriology—*Haverhillia multiformis* was recovered from the blood in pure culture on seven occasions while the patient was in the hospital on Nov 20, 1937, 15 colonies per cubic centimeter, on December 7, 18 colonies, on December 8, 19 colonies, on December 9, 22 colonies, on Jan 4, 1938, 19 colonies, on January 5, 23 colonies, and on January 7, 6 colonies Subsequent to the patient's discharge cultures of blood taken on April 12 and June 14 were sterile

The micro-organisms isolated corresponded in every particular tested with the organism of Parker and Hudson² The marked pleomorphism was its most striking characteristic (fig 2) Coccobacilli, rods, filaments and threads were all on occasions encountered in a single oil immersion field, and round or fusiform swellings situated in any portion of the rod were frequently seen Distinct branching was noted The micro-organism varied in length from 2 to 15 microns and in width from 0.2 to 0.5 micron The diameter of the swellings ranged from 2 to 6 microns In blood broth the rods and filaments were often seen in tangled masses

Haverhillia multiformis is gram-negative, not acid-fast and not encapsulated No motility was observed in hanging drop or in dark field preparations

On whole human blood agar, as well as in 0.1 per cent dextrose beef heart infusion broth (p_H 7.8) to which human blood had been added, the organism grew extremely well The optimal temperature range for growth was 35 to 38 C Good growth was obtained aerobically Only fair proliferation was obtained on chocolate agar, and no growth occurred on plain agar or in 0.1 per cent dextrose beef infusion broth Blood, serum, ascitic fluid or egg yolk furnished the indispensable growth factors

In serum or ascitic fluid broth the growth appeared at the bottom of the tube as a gray-white layer made up of small particles of aggregated organisms Colonies developing in the broth on the side of the tube appeared as soft white fluffy aggregates which were not easily broken up The supernatant broth remained clear, and no pellicle was observed

The surface colonies on semisolid mediums were round, regular, soft and moist, ranging from 1 to 2 mm in diameter Usually they were discrete, but on very moist mediums some confluence was observed

Intraperitoneal inoculation of 2 white mice with 0.5 cc of a forty-eight hour blood broth culture resulted in the death of one mouse in twenty-four hours and of the other mouse in forty-eight hours After death *Haverhillia multiformis* was seen in direct smear and recovered in pure culture from the peritoneal fluid and from the heart's blood

The patient's serum collected in the fifth week of disease agglutinated her own organism completely in dilutions ranging from 1:20 to 1:640

References to other cultural characteristics are available in the article of Parker and Hudson² and the book of Topley and Wilson⁴ One interesting characteristic of the organism is its specific pathogenicity for

4 Topley, W. W. C., and Wilson, G. S. The Principles of Bacteriology and Immunity, Baltimore, William Wood & Company, 1936, pp. 274 and 997

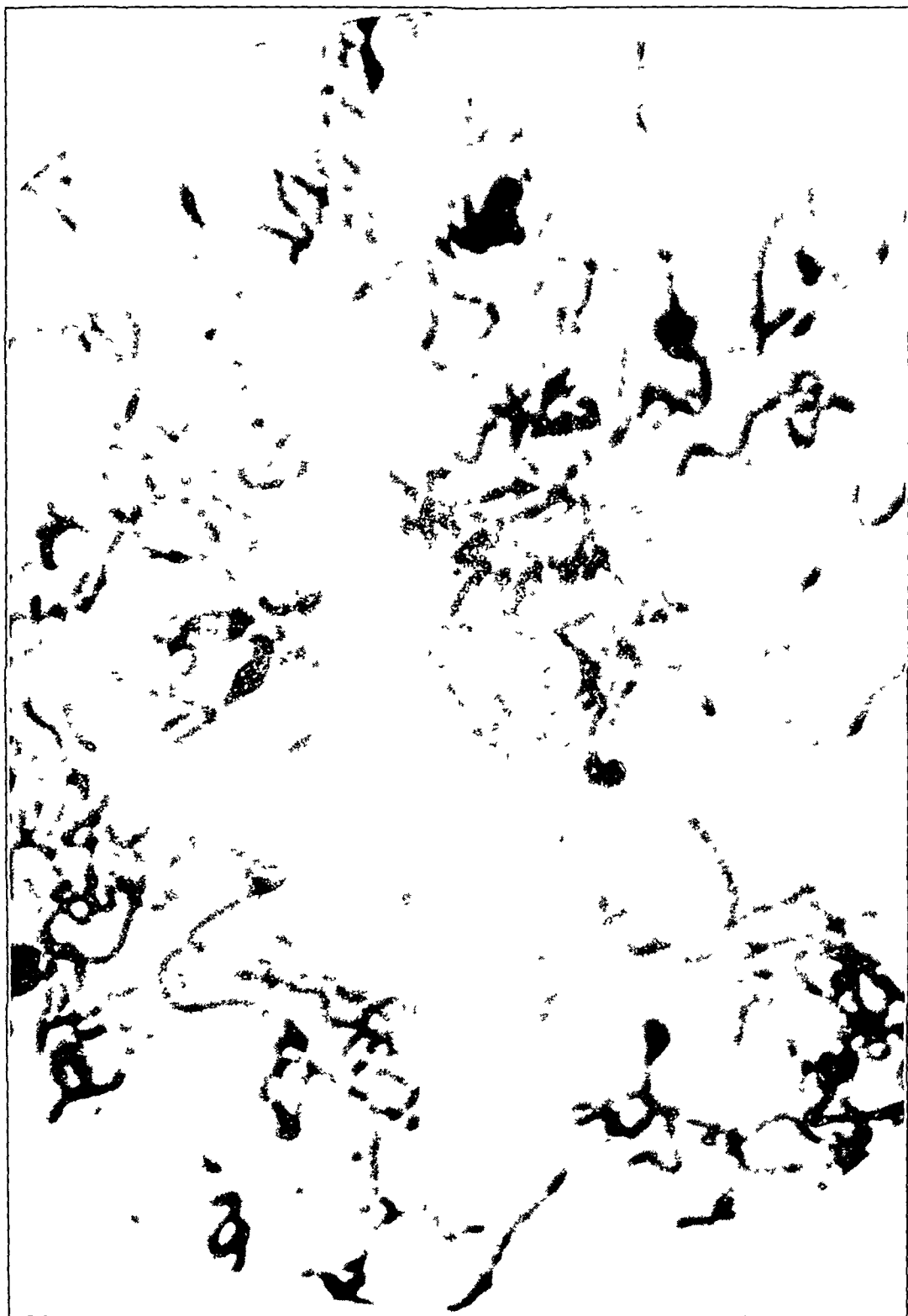


Fig 2.—*Haverhillia multiformis* (Parker and Hudson²) obtained by forty-eight hour culture in whole blood agar. Magnification, $\times 2,700$. Note streptobacillary and branching forms.

mice, in which it causes an epizootic, with arthritis as a prominent manifestation of the infection ⁵

HISTORICAL REVIEW

The condition we have just described was apparently first recognized by Schottmuller ⁶ in 1914. Since this time other cases have been reported which were not linked with his, and other names have been assigned both to the clinical syndrome and to the organism. As a result, case reports are now hidden in the literature under a variety of headings. It is instructive to bring together these scattered case reports for comparison with our own, as presented in the accompanying table. In our series we include only those cases in which an organism closely resembling *Haverhillia multiformis* (Parker and Hudson, 1926 ²) has been demonstrated on culture of blood or joint fluid.

In 1914 Schottmuller ⁶ reported 2 cases of *Bisskrankheit*, but positive blood cultures were obtained only in the first of these cases, hence only the first case will be considered here. In the patient, a laboratory *Diener*, there developed, following rat bite, a local lymphadenitis and lymphangitis with fever and considerable pain and tenderness in muscles of the left arm and leg. Movement of the left shoulder caused exquisite pain. It is interesting that the bite occurred not on the left but on the right thumb. A roseola-like exanthem was observed on the arms, legs and abdomen seven days after the bite. This eruption faded within sixteen days. The patient's temperature was 39.3 C (102.7 F) on admission to the hospital, seven days after the bite. It was remittent, tending to fall to a lower level each successive day until the sixteenth day after the bite, when a sharp rise occurred, accompanied by exacerbation of symptoms. The temperature subsequently fell slowly to a normal level, and the patient was eventually discharged well after a stay of nearly ten weeks in the hospital. Eight blood cultures taken during this period were positive for an organism Schottmuller named *Streptothrix muris ratti*. Growth occurred, apparently under aerobic conditions, on Löffler's serum medium and on milk agar but not on other culture mediums. The organism was described as gram-positive (*nach der Gramschen Methode blau tingiert*).

5 (a) Levaditi, C., Selbie, R. F., and Schoen, R. Le rhumatisme infectieux spontané de la souris provoqué par le *Streptobacillus moniliformis*, Ann Inst Pasteur **48** 308, 1932. (b) Mackie, T. J., van Rooyen, C. E., and Gilroy, E. An Epizootic Disease Occurring in a Breeding Stock of Mice. Bacteriological and Experimental Observations, Brit J Exper Path **14** 132, 1933. (c) van Rooyen, C. E. The Biology, Pathogenesis and Classification of *Streptobacillus Moniliformis*, J Path & Bact **43** 455, 1936. (d) Topley and Wilson ⁴

6 Schottmuller, H. Zur Aetiologie und Klinik der Bisskrankheit, Dermat Wehnschr (supp) **58** 77, 1914

*Sporadic Instances of Haverhill Fever Proved by Cultivation of an Organism Resembling Haverhillia Multiformis
from Peripheral Blood or from Joint Fluid*

Case No	Report			Patient			Apparent Mode of Infection	Disease		Characteristics of Organism		
	Year	Author	Locality	Sex	Age	Occupation		Designation Given Disease	Name Given Organism	Pleomorphism	Growth on Gram Stain	Outcome
1	1914	Schottmüller	Hamburg, Germany	Male	25 yr	Laboratory servant	Rat bite	Blisskrankheit	<i>Streptothrix muris rattii</i>	+	+	Recovered
2	1916	Blake	Boston	Female	67 yr	Shopkeeper	Rat bite	Rat bite fever	<i>Streptothrix muris rattii</i>	+	—	Died, autopsy
3	1917	Litterer	Nashville	Male	14 yr ?		Rat bite	Rat bite fever	<i>Streptothrix longus</i>	+	±	Recovered
4	1917	Litterer	Nashville	Male	5 yr		Rat bite	Rat bite fever	<i>Streptothrix brevis</i>	+	±	Recovered
5	1918	Dick and Tunncliff	Chicago	Male	10 yr		Weasel	Typical of rat bite fever	<i>Streptothrix putorii</i>	+	—	Recovered
6	1918	Tunncliff and Mayer	Chicago	Female	13 days		Rat bite	Rat bite fever	Closely related to <i>Streptothrix putorii</i>	+	—	Died, autopsy
7	1925	Ebert and Hesse	Leningrad, U S S R	Female	42 yr	Teacher	Rat bite	Japanisches Rattenbissfieber	<i>Streptothrix muris rattii</i>	+	?	Recovered
8	1925	Levaditi, Nicolau and Poineloux					Obscure	Érythème polymorphe aigu	<i>Streptobacillus moniliformis</i>	+	—	Recovered
9	1926	Dodd	Baltimore	Female	10 yr		Rat bite	Erythema arthriticum epidemicum	Not identified but from description <i>streptothrix</i>	+	—	Recovered
10	1929	Tessier, Rivallier, Reilly and Garnier	Paris, France	Female	35 yr	Writer	Obscure	Érythème infectieux	<i>Streptobacillus moniliformis</i>	+	—	Recovered
11	1932	Hazard and Good-kind	Boston	Male	58 yr		Obscure	Haverhill fever	<i>Haverhillia multiformis</i>	+	—	Recovered
12	1934	Scharles and Sea stone	Boston	Male	25 yr ?	Medical student	Rat bite	Haverhill fever	<i>Haverhillia multiformis</i>	+	—	Recovered
13	1937	Lemierre, Reilly, La-Porte and Morin	Paris, France	Male	40 yr	Railway worker	Rat bite	Fèvre par morsure de rat	<i>Streptobacillus moniliformis</i>	+	—	Recovered
14	1938	Farrell, Lordi and Vogel	Brooklyn	Female	40 yr	Housewife	Rat bite	Haverhill fever	<i>Haverhillia multiformis</i>	+	—	Recovered

In 1916 Blake ⁷ reported a fatal infection with *Streptothrix muris ratt* following rat bite. Autopsy disclosed acute ulcerative endocarditis of the mitral valve, with infarcts lodged in the spleen and kidney. The organism was recovered from the blood of the patient during life and from heart's blood post mortem. In the same year Tileston ⁸ reported 2 cases of "rat-bite fever," in each case basing his diagnosis on the history of rat bite and on the clinical course, which was characterized by periodic fever. In 1 case he observed rodlike forms in the peripheral blood during the febrile paroxysms, but failure to cultivate this possible "streptothrix" necessitates exclusion of the report from this series.

In 1917 Litterer ⁹ reported 2 additional cases, in both of which the disease followed rat bite and in both of which he established the diagnosis by blood culture. Minor differences in the organisms recovered led him to assign different specific names to the two strains he isolated, but their essential similarity with Schottmuller's organism is apparent from his descriptions.

In 1918 Dick and Tunnichiff ¹⁰ and Tunnichiff and Mayer ¹¹ reported the fifth and sixth cases of apparent *Haverhillia multiformis* infection. In 1 of their cases the disease followed weasel bite, in the other, in which death ensued and autopsy was done, it occurred after rat bite. From blood culture, in both instances a "streptothrix" was grown, variations in the cultural characteristics of which again led to new terminology, which is listed in the table.

In 1925 Ebert and Hesse ¹² reported isolation of an organism showing great similarity (*grosse Ahnlichkeit*) to the organisms of Schottmuller and of Blake in a case of a disease they described as *japanisches Rattenbissfieber* (sodoku). In the same year Thorp ¹³ gave an extremely incomplete account of a case of fever following rat bite, with isolation of a "leptothrix" in material from swellings which developed on each wrist and near the sternoclavicular joints. The case is not included in our series because there is no report of blood culture and the history is inadequate.

7 Blake, F. G. The Etiology of Rat-Bite Fever, *J. Exper. Med.* **23** 39, 1916.

8 Tileston, W. The Etiology and Treatment of Rat-Bite Fever, *J. A. M. A.* **66** 995 (April 1) 1916.

9 Litterer, W. A. Study of the *Streptothrix* Isolated in Two Cases of Rat-Bite Fever, *Tr. Sect. Path. & Physiol., A. M. A.*, 1917, p. 275.

10 Dick, G. F., and Tunnichiff, R. A *Streptothrix* Isolated from the Blood of a Patient Bitten by a Weasel (*Streptothrix Putorii*), *J. Infect. Dis.* **23** 183, 1918.

11 Tunnichiff, R., and Mayer, K. M. A Case of Rat-Bite Fever, *J. Infect. Dis.* **23** 555, 1918.

12 Ebert, B., and Hesse, E. Zur Klinik und Bakteriologie des japanischen Rattenbissfiebers (Sodoku), *Arch. f. klin. Chir.* **136** 69, 1925.

13 Thorp, E. Rat-Bite Fever in an Infant, *Brit. M. J.* **2** 255, 1925.

In 1925¹⁴ (final report, 1926¹⁵) Levaditi, Nicolau and Poincloux described a case in which the clinical course was characterized by remittent fever with a four to six day cycle. There was no history of rat bite. Three febrile paroxysms were experienced, following each of which there appeared a maculopapular eruption, chiefly on the limbs. Severe pain developed in the left ankle and in the right acromioclavicular joint. Recovery was complete. On two occasions there was isolated in blood culture an organism they named *Streptobacillus moniliformis*. No reference was made to Schottmuller's organism or to the series of cases which had been appearing as instances of rat bite fever. Attention was focused on the dermatologic aspects of the infection, and the condition was described as acute erythema multiforme (*érythème polymorphe aigu*).

These 8 case reports described sporadic instances of Haverhillia multiformis infection, but in 1926 Place, Sutton and Willner¹⁶ under the designation erythema arthriticum epidemicum (final report by Place and Sutton, 1934¹) reported an epidemic of 86 cases of what seems to have been the same infection, and in 12 of these cases Parker and Hudson isolated from blood or from joint fluid the organism they named Haverhillia multiformis. "slender, gram-negative and non acid resisting rods staining with some difficulty, often forming threads and showing tendency toward branching, marked irregularity of form with swellings and enlargements, fermentation of some carbohydrates, in general, requiring blood or ascitic fluid for growth"² These epidemic cases were not associated with rat bite and were not at the time identified with the earlier isolated cases we have cited. Dodd,¹⁷ however, in the same year (1926), under the name erythema arthriticum epidemicum, reported a case of disease following rat bite which she had observed in Baltimore in 1923, making a retrospective diagnosis. The organism was incompletely studied.

In 1929 Teissier, Rivalier, Reilly and Garnier¹⁸ reported a case of "infectious erythema" with isolation of *Streptobacillus moniliformis* on blood culture. There was no history of rat bite.

14 Levaditi, C, Nicolau, S, and Poincloux, P. Sur le rôle étiologique de streptobacillus moniliformis (nov spec) dans l'érythème polymorphe aigu septicémique, Compt rend Acad d sc **180**:1188, 1925

15 Levaditi, C, Nicolau, S, and Poincloux, P. Recherches sur l'étiologie de l'érythème polymorphe aigu, son agent étiologique, Streptobacillus moniliformis, Presse méd **34** 340, 1926

16 Place, E H, Sutton, L E, and Willner, O. Erythema Arthriticum.Epidemicum. Preliminary Report, Boston M & S J **194** 285, 1926

17 Dodd, K. An Isolated Case of Erythema Arthriticum Epidemicum, Boston M & S J **194** 633, 1926

18 Teissier, P, Rivalier, E, Reilly, J, and Garnier, G. Sur un cas d'érythème infectieux du au "Streptobacillus moniliformis," Congres de dermatologistes et syphiligraphes de langue franç, Paris, Masson & Cie, 1929, p 73

In 1932 Hazard and Goodkind¹⁹ gave the first complete report of a sporadic case of a disease identified at the time as Haverhill fever (erythema arthriticum epidemicum) with recovery of *Haverhillia multiformis* on blood culture. They obtained no history of rat bite, but in 1934 Scharles and Seastone²⁰ described a case of rat bite infection in a medical student in which diagnosis had been made by cultivation of *Haverhillia multiformis* from joint fluid.

The most recent case report previous to our own came from France, that of Lemierre, Reilly, LaPorte and Morin,²¹ who in 1937 described a case of *fièvre par morsure de rat* with recovery from the blood stream of *Streptobacillus moniliformis*. Infection with Levaditi's organism was thus finally allied with the *Bisskrankheit* of Schottmuller.

COMMENT

Bacteriology—Our first question is, are all these organisms the same? Without type cultures for comparison or cross immunity tests, no proof, of course, can be offered, nor will proof of this kind ever be available in all the cases of this series. A number of authors²² have regarded *Streptothrix muris ratt*i (Schottmuller, 1914), *Streptobacillus moniliformis* (Levaditi and others, 1926) and *Haverhillia multiformis* (Parker and Hudson, 1926) as closely related if not identical strains. Others²³ have identified *Streptobacillus moniliformis* with *Haverhillia multiformis* without reference to Schottmuller's organism. The fact that his organism was gram-positive and the other organisms in this series gram-negative seems sufficiently explained by Litterer,⁹ who remarked that the variability in staining reaction seemed dependent on the age of the culture. Slight morphologic distinctions or differences in sugar fermentation reactions seem unimportant when contrasted with the two major characteristics common to this group: extreme pleomorphism of an unusual type and special growth requirements. All these organisms, except that of Dick and Tunnichiff,¹⁰ can fairly be

19 Hazard, J. B., and Goodkind, R. Haverhill Fever (Erythema Arthriticum Epidemicum). A Case Report and Bacteriologic Study, *J. A. M. A.* **99** 534 (Aug. 13) 1932.

20 Scharles, F. H., and Seastone, C. V., Jr. Haverhill Fever Following Rat-Bite, *New England J. Med.* **211** 711, 1934.

21 Lemierre, A., Reilly, J., Laporte, A., and Morin, M. Sur une nouvelle fièvre par morsure de rat, *Bull. Acad. de méd., Paris* **117** 705, 1937.

22 (a) Dienes, L., and Edsall, G. Observations on the L-Organism of Kheneberger, *Proc. Soc. Exper. Biol. & Med.* **36** 740, 1937. (b) Place and Sutton.¹ (c) Topley and Wilson.⁴

23 Levaditi, C. À propos de l'étiologie de l'érythème polymorphe infectieux contagieux et épidémique, *Presse méd.* **36** 65, 1928. van Rooyen^{5c} Teissier and others.¹⁸ Lemierre and others.²¹

described in the words of Parker and Hudson² as "in general, requiring blood or ascitic fluid for growth"

Three conflicting views have been taken regarding classification of this unusual organism. Schottmuller regarded it as an actinomyces, as did Parker and Hudson, and Topley and Wilson unhesitatingly assigned it to this order. Levaditi placed it among the bacteria, while Klieneberger,²⁴ in work recently supported by Dienes and Edsall,^{22a} maintained that the form previously regarded as single in truth consists of a streptobacillus growing in symbiosis with a rounded, coccoid, "pleuro-pneumonia-like organism"^{24a} the "L₁ organism of Klieneberger"^{22a}. The latter symbiont forms the knobs and fusiform swellings hitherto looked on simply as pleomorphic changes. Van Rooyen,^{5c} like Parker and Hudson,² stressed the organism's special growth requirements but failed to find true branching. He stated that he looked on it as a single pleomorphic organism of the family Bacteriaceae, tribe Haemophilaeae, genus *Haverhillia*, type species *Haverhillia multiformis* (Parker and Hudson). The literature as we interpret it gives priority to Schottmuller's name for this organism, but as his term, *Streptothrix muris rattii*, is now unacceptable for taxonomic reasons, the term of Parker and Hudson seems more satisfactory until the difficult question of classification has been authoritatively decided.

Clinical Syndrome—The reports summarized here have fallen into three clinical groups, and it seems convenient to discuss them under the designations originally applied.

Rat Bite Fever Of the cases reviewed, in 10 there was a history of rat bite and in 1 of weasel bite, of these cases, 7 were looked on as instances of rat bite fever, Schottmuller carefully naming the condition in his case simply "bite disease". Continued use of the term "rat bite fever" to describe instances of *Haverhillia multiformis* infection is ill advised, for the term is also in use to describe *Spirillum minus* infection,²⁵ or sodoku. The etiologic agents of these two diseases are distinct—the one, *Haverhillia multiformis*, being a nonmotile pleomorphic bacillus which grows on serum mediums, the other, a highly motile spirillum of uniform morphologic character which has never²⁶ been

24 Klieneberger, E. (a) The Natural Occurrence of Pleuro-Pneumonia-Like Organisms in Apparent Symbiosis with *Streptobacillus Moniliformis* and Other Bacteria, *J Path & Bact* **40** 93, 1935, (b) Further Studies on *Streptobacillus Moniliformis* and Its Symbiont, *ibid* **42** 587, 1936.

25 Robertson, A. *Spirillum Minus* (Carter 1887), the Aetiological Agent of Rat-Bite Fever. A Review, *Ann Trop Med* **24** 367, 1930. McDermott, E. M. Rat-Bite Fever. A Study of the Experimental Disease, with a Critical Review of the Literature, *Quart J Med* **21** 433, 1928.

26 Bayne-Jones, S. Rat-Bite Fever in the United States, *Internat Clin* **3** 235, 1931.

successfully cultivated outside the animal body. Either infection may follow rat bite, but while *Haverhillia multiformis* infection has occurred without a history of rat bite, no example of *Spirillum minus* infection has been found in which a history of antecedent rat bite or an account of close contact with rats or with associated animals was lacking. Haverhill fever has caused at least one epidemic, sodoku has never occurred except in sporadic form. Haverhill fever is accompanied by painful arthritis and is resistant to treatment, sodoku is not characterized by articular involvement, and arsenical therapy has a specific curative effect. Both infections have cutaneous manifestations,²⁷ but one is essentially embolic, the other primarily allergic. Haverhill fever may be characterized by a continued remittent fever or by an intermittent fever with a four to six day periodicity. The febrile reaction in sodoku is characteristically only of the latter type. No one has explained why the temperature charts of these two infections with entirely different causal agents should at times exactly resemble each other, particularly when the fever is of a distinctive, periodic type found rarely, if at all, in any other clinical condition. The type of fever is so unusual that in the past numerous authors have considered a history of rat bite followed by an intermittent fever with a four to six day periodicity sufficient grounds for a case report labeled "Rat Bite Fever." Coincident infection with *Haverhillia multiformis* and *Spirillum minus* is theoretically possible,¹² but it has never been proved. Mackie and McDermott²⁸ suggested the possibility in their case, but examination of their data shows that they were dealing with some organism other than *Haverhillia multiformis* in association with the spirillum of sodoku. Elucidation of the exact bacteriologic relation between *Haverhillia multiformis* and *Spirillum minus* and of the clinical affinities of Haverhill fever and sodoku must await longer observation. Sufficient knowledge is at hand, however, to differentiate the two bacteriologically, and it is unfortunate that three American medical textbooks published during 1937 and 1938 confuse the bacteriologic entity of *Spirillum minus* infection with infection due to *Haverhillia multiformis* because of the common association with rat bite and certain clinical similarities.

Erythema (Polymorphous, Infectious, Arthritic). Levaditi and his co-workers¹⁴ were the first to consider *Haverhillia multiformis* infection as one of the erythemas, but Place, Sutton and Willner¹⁶ independently adopted the same point of view, and the cases of the

27 O'Leary, P. A. The Dermatologic Aspects of Rat-Bite Fever, *Arch Dermat & Syph* 9 293 (March) 1924.

28 Mackie, T. J., and McDermott, E. N. Bacteriological and Experimental Observations on a Case of Rat-Bite Fever. *Spirillum Minus*, *J Path & Bact* 29 493, 1926.

Haverhill epidemic were originally described by them as examples of erythema arthriticum epidemicum. An important American textbook of medicine published in 1937 classifies *Haverhillia multiformis* infection with the erythemas, listing it with types such as erythema nodosum and erythema infectiosum. This conception of the disease as a dermatologic condition is inadequate, the cutaneous eruption is simply one manifestation of primary septicemia, and the disease is not just a local condition but a general systemic infection.

Haverhill Fever—This term was in popular use to describe the cases of the Haverhill epidemic before the cause of the disease was known. We have preferred it because it properly emphasizes the systemic nature of the infection and because it is applicable in sporadic as well as epidemic cases.

Epidemiology—There are two known modes of infection with *Haverhillia multiformis*: rat bite⁶ and ingestion of raw milk¹ which has been contaminated with the organism. Rats are known to harbor the organism in the nasopharynx²⁹ as a benign inhabitant or in the lungs³⁰ as an apparent pathogen associated with bronchopneumonia. An obvious possibility in accounting for the Haverhill epidemic is that rats had access to the milk supply.

Differential Diagnosis—The history of rat bite or the periodic fever may suggest sodoku, diagnosis of which requires demonstration of *Spirillum minus* in the patient's blood or in the material aspirated from the local lesion at the site of the rat bite or from the regional lymph nodes. Inoculation of 1 cc of whole blood intraperitoneally or subcutaneously into white mice free³¹ from *Spirillum minus* infection will ordinarily, after an incubation period of ten days or longer, result in a blood stream infection that will continue for months, and diagnosis can readily be made by dark field examination. In *Haverhillia multiformis* infection the fever may be of the continued type and may resemble the fever of any infectious or septic condition. The arthritis may suggest undulant fever or rheumatic fever or may be regarded as infectious arthritis of another type. The eruption may be confused with one of the erythemas (infectious erythema or erythema multi-

29 Strangeways, W. I. Rats as Carriers of *Streptobacillus Moniliformis*, J Path & Bact **37** 45, 1933. Lemierre and others²¹

30 Tunnickliff, R. Streptothrix in Bronchopneumonia of Rats Similar to That in Rat-Bite Fever, J Infect Dis **19** 767, 1916. Kheneberger, E., and Steabben, D. B. On a Pleuropneumonia-Like Organism in Lung Lesions of Rats, J Hyg **37** 143, 1937.

31 Knowles, R., Das Gupta, B. M., and Sen, S. Natural *Spirillum minus* Infection in White Mice, Indian M Gaz **71** 210, 1936. Francis, E. Rat-Bite Fever Spirochetes in Naturally Infected White Mice, *Mus Musculus*, Pub Health Rep **51** 976, 1936.

forme), or the entire picture may be attributed to one of the eruptive fevers. The final diagnosis rests on culture of blood or of joint fluid.

Treatment—Neoarsphenamine has been used with apparent success in cases of *Haverhillia multiformis* infection with periodic fever. In 2 cases in which there was periodic fever the condition responded to autogenous vaccine, according to Litterer.⁹ In cases in which there was continued fever, no therapy seems to have been effectual. If, as some have maintained, the organism is one of the actinomycetes, further trial of thymol in larger doses seems justifiable.

SUMMARY

Clinical and bacteriologic findings in the fourteenth sporadic case of Haverhill fever to be reported are presented.

Previous case reports are reviewed.

The bacteriology, clinical syndrome, epidemiology, differential diagnosis and treatment of this disease are discussed.

Dr. M. L. Rakieten first suggested the identity of the organism isolated in the case we have reported.

The photograph is the work of Mr. S. Montes.

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A REVIEW OF MENINGITIS DUE TO MICROCOCCUS TETRAGENUS

REPORT OF ONE CASE WITH BACTERIOLOGIC STUDY

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Although Gaffke described *Micrococcus tetragenus* in phthisical sputum in 1881, the finding of this organism in the spinal fluid is still rare. A search of all the indexed journals discloses only 7 prior cases in the accumulated world literature. Probably the diagnosis of meningitis due to this organism is frequently missed in this country because the symptoms, physical and laboratory findings and clinical course are similar to those of meningococcic meningitis. Reimann¹ in 1934 stated that there were only 2 or 3 reports of any form of infection by *M. tetragenus* in American literature, in contrast to 170 cases reported in European publications. In recording this case, the eighth, and analyzing the preceding cases, we hope to emphasize sufficiently the similarity to infection with meningococci or staphylococci and to point out the inherent characteristics peculiar to *M. tetragenus*. A realization of these facts should result in the recognition of the condition in an increasing number of cases in the future.

From the United States Penitentiary Hospital, through the courtesy of Dr O C Williams, United States Public Health Service, Medical Officer in Charge. The bacteriologic studies were carried out in the laboratory of the Station Hospital, Fort Leavenworth, Kan., Captain D C Kuhns, Medical Corps, United States Army, in charge.

1 Reimann, H A (a) *Micrococcus Tetragenus* Infection. Review of Literature and Report of a Case, *J Clin Investigation* **14** 311 (May) 1935, (b) Bacterial Type Dissociation of *Micrococcus Tetragenus* Infection. II. Description of Variant Forms, *J Bact* **31** 385 (April) 1936, III. Immunologic Studies of Variant Forms, and Discussion, *ibid* **31** 407 (April) 1936, Bacterial Type Transformation. *Micrococcus Tetragenus* Infection, *ibid* **33** 499 (May) 1937, Variation of *Micrococcus Tetragenus*, *Proc Soc Exper Biol & Med* **34** 344 (April) 1936, Transformation of Bacterial Types, *ibid* **35** 64 (Oct) 1936.

It is well known that *M. tetragenus* is a common inhabitant of the nose, throat and sputum of patients with tuberculosis. Although it is frequently seen in smears of material from the throat or of sputum, it has been regarded as a nonpathogenic organism, nevertheless, it becomes invasive when the general resistance is lowered. In our case meningitis is thought to have followed invasion of the blood stream by the organism, despite a negative blood culture and the possibility of direct extension from the nasopharynx.

REPORT OF CASE

Clinical History—On July 16, 1936, D. H., an inmate of the United States Penitentiary, a white man aged 20, lapsed into unconsciousness suddenly while working in the "yard gang." Since the weather had been extremely humid for a number of days, with daily temperature peaks over 100 F, it was assumed on his admission to the prison hospital that he was suffering from heat exhaustion. He soon revived on symptomatic treatment and stated that he had had pains in the neck and general malaise for ten days. Aside from several minor injuries, the past history was irrelevant.

Physical Examination—At the time of admission he appeared comatose and acutely ill. Neurologic examination showed hyperactive cremasteric, abdominal and Brudzinski reflexes on the right side, contrasted with hypoactive reflexes on the left. The muscles of the neck were rigid, and a definite Kernig sign was present. The pupils were equal and regular and reacted to light. All other physical findings were normal. The nasal and pharyngeal mucous membranes were not inflamed. The clinical impression was heat exhaustion.

Course of the Disease—On the morning following the admission stiffness of the neck, headache and abnormal reflexes had disappeared, the patient was conscious and rational and, but for a slight elevation of temperature (38 C) [100.4 F], appeared to be recovering from his supposed attack of heat exhaustion.

In the afternoon of the second day in the hospital the picture changed. The temperature rose to 38.7 C (101.7 F), and the patient began to complain of a bitemporal headache, with pains in the back of his neck. A Kernig and a Brudzinski sign reappeared at the same time. The symptoms now were indicative of definite meningeal involvement, and since there had recently been a case of meningococcic meningitis in the hospital it was assumed that the meningococcus was again the causative organism.

Treatment and Laboratory Findings—A lumbar puncture was done, the spinal fluid was cloudy and under increased pressure (280 mm of water). This observation enhanced the assumption that the condition was of meningococcic origin, accordingly, 30,000 units of antimeningococcus serum was given intrathecally in divided doses, with 20 cc of antitoxin intramuscularly, during the next twelve hours. For the next seven days 10,000 units of the antiserum and 10 cc of antitoxin were given daily. Spinal fluid was drained eleven times thereafter at appropriate intervals for the relief of pressure symptoms.

Examination of the original specimen of spinal fluid showed a cell count of 5,300 per cubic millimeter, with a differential count of 94 per cent neutrophils and 6 per cent lymphocytes, the reaction for globulin to Pandy's reagent was 4 plus, quantitative determinations showed a decrease in sugar and the colloidal gold test resulted in a curve typical of purulent meningitis (0000244444). A direct smear with Gram stain revealed diplococci, some of which were gram-positive and resembled meningococci in structure but were not intracellular. Cultures made on this and the following two days gave pure growths of gram-positive tetrads.

Serum Reaction—There is no specific antiserum for *M. tetragenus*, since the organism was agglutinated with dilutions up to 1:180 by polyvalent antimeningococcus serum, administration of antiserum was continued up to the ninth day,

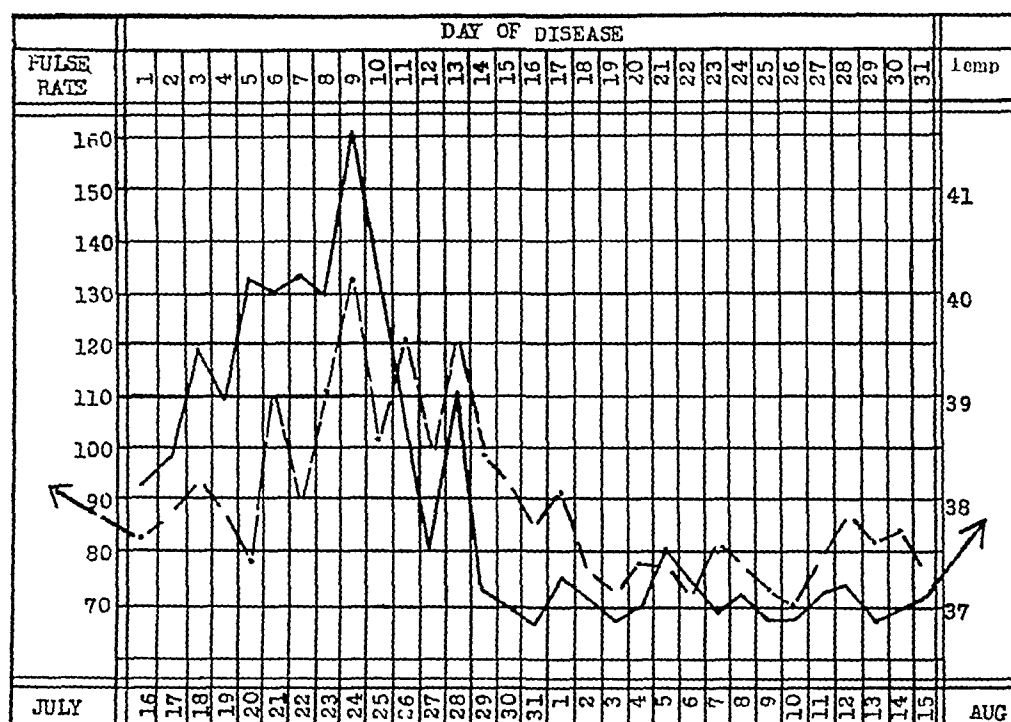


Chart 1—Pulse rate and temperature

when suddenly difficulty in breathing and a rapid, thready pulse developed. In the course of the day there appeared petechiae on the lower extremities, general adenitis, an urticarial rash over the entire body, functional heart murmur and cyanosis. The patient became irrational and semicomatose. These findings were interpreted as manifestations of serum sickness. Although the prognosis appeared grave, he improved rapidly, his temperature receded to normal on the fifteenth day and remained within normal limits thereafter until the day of discharge, August 28. Since then he has been normal in every way.

It will be noted in chart 1 that the temperature corresponded to that in cases of typical meningococcic meningitis. It varied according to the degree of toxemia and reflected the general condition of the patient. It reached a peak of 41.5 C (106.7 F) on the ninth day, gradually returned to normal on the fifteenth day and remained within normal limits thereafter.

The variation of the pulse concided almost exactly with that of the temperature. It is worthy of note that the pulse was slow in relation to the degree of fever for the first seven days, during which time the patient exhibited other signs symptomatic of intercerebral pressure, namely, headache, vomiting, mental confusion and stupor. Reference to chart 2 shows that for the first seven days the pressure at the lumbar level, with the patient in the horizontal position, varied between 350 and 280 mm of water, with the cell count elevated as high as 15,000 per cubic millimeter. Coincidentally with a marked improvement in the general condition and rapid fall toward normal for the spinal fluid pressure and cell count, the pulse rate became proportional, its curve crossed the temperature line, and it remained slightly faster during convalescence.

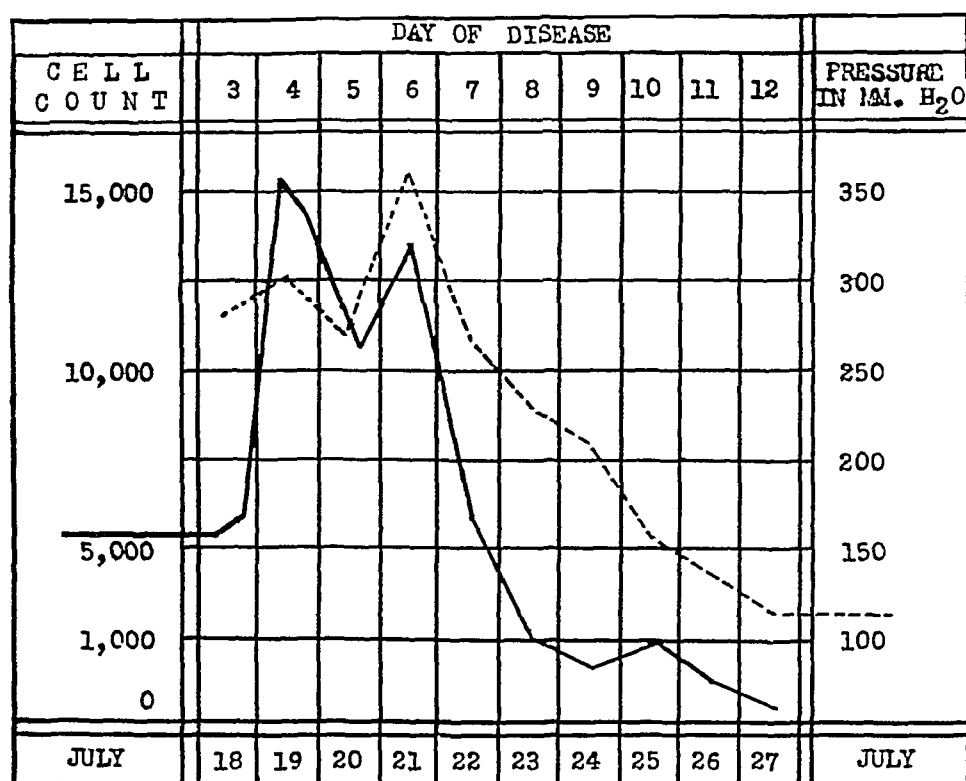


Chart 2—Data on spinal fluid

Laboratory Observations—The urine was normal in all respects. The erythrocyte count and hemoglobin concentration were within the accepted limits. The Wassermann and the Kahn test were negative. The leukocytes ranged between 18,000 and 20,000 per cubic millimeter the first eight days, with a decided shift to the left in the Schilling index. On the fifth day 81 of the 96 per cent granulocytes were nonfilamented forms or younger. The granulocytes predominated throughout the disease. The spinal fluid pressure and cell count fell toward normal just as the Schilling index shifted back to the right, and the total leukocyte count dropped below 10,000 per cubic millimeter. The reaction for globulin remained 4 plus to Pandy's solution through the ninth day.

Cutaneous Reactions—Early in the disease the patient was tested intradermally with soluble meningococcus toxin with the dilutions and on the dates outlined in table 1. The skin test dose was 0.05 cc intracutaneously.²

The patient was tested by means of intracutaneous wheals to determine his sensitivity to the meningococcus toxin. It was found he reacted even with the dilution of 1:100,000. After the administration of the antimeningococcus serum throughout

TABLE 1—*Intradermal Tests with Soluble Meningococcus Toxin*

Dilutions of Toxin	Dates Administered, 1936		
	July 17 1st Day of Disease	July 21 4th Day of Disease	July 23 8th Day of Disease
1:100,000	+ — (—)	Negative	Negative
1:10,000	+ — (—)	Negative	Negative
1:1,000	+ — (+)	Negative	Negative
1:100	+	+ —	Negative
1:10	++	+	+ —
Full strength	+++	++	+

TABLE 2—*Analysis of the Eight Reported Cases of Meningitis Due to M. Tetragenus*

Case No.	Age	Sex	Onset	Duration, Wk.	Outcome	Early Manifestation	Complications and Sequelae	Predisposing Factor
1	32	F	Not given	Not given	Death	Puerperal infection	Septicemia	Childbirth
2	35	M	Sudden	3	Death	None described	None described	None described
3	48	F	Sudden	5	Death	None described	None described	None described
4	?	M	Sudden	2	Recovery	Sudden headache and general malaise	Pulmonary infection	Disease of the upper respiratory tract
5	23	M	Sudden	1	Death	Sore throat and malaise	Septicemia and arthritis	Disease of the upper respiratory tract
6	28	M	Sudden	4	Recovery	Believed to be brucellosis	None described	None described
7	46	M	Sudden	2	Recovery	Painful joints and sore throat	Pharyngitis, arthritis and septicemia	Drunken debauch and disease of the upper respiratory tract
8	20	M	Sudden	2	Recovery	Pain in neck and general malaise	Serum sickness	Heat exhaustion

the disease it was found that he reacted only weakly to the strongest concentrations—plus-minus to 1:10 on July 23, 1936, the eighth day of the disease. The sole significance of this is that immunity to the soluble toxin of the meningococcus may create an immunity to the soluble toxin of *M. tetragenus* also, since the decrease in cutaneous reactivity did parallel recovery from the disease.

² Kuhns, D. M. Control of Meningococcic Meningitis Epidemics by Active Immunization with Meningococcus Soluble Toxin, J. A. M. A. **107**: 5 (July 4) 1936.

COMPARISON OF EIGHT CASES OF MENINGITIS DUE TO *M. TETRAGENUS*

The following cases of meningitis due to *M. tetragenous* have been reported

Case Number	Source
1	Benzancon and Lepage ³
2	Grieve, Fackler and Mitchell ⁴
3	Pende ⁵
4	Vincent ⁶
5	Leschke ⁷
6	Bonanno ⁸
7	Reimann ^{1a}

In comparing the clinical features of this case with those of 7 reported cases (table 2), we see that in all the condition had a sudden onset and that the shortest duration was one week and the longest five weeks. Four of the patients made an uncomplicated neurologic recovery, which is in decided contrast to the residuum which meningococcic meningitis so often leaves.

A much larger series of cases will be necessary before statistical significance can be placed on the sex or age distribution. In this small series the sex ratio showed male predominance by 3 to 1. Strangely enough, all attacks were in the virile adult decades, leaving untouched the debilitated aged and the immature. For an organism looked on as nonpathogenic or feebly virulent at most, such an age incidence cannot be explained satisfactorily with the present small series. Perhaps the distribution depends solely on the presence of a conditioning or predisposing factor which has made the subject unusually susceptible. This factor has been reported in a majority of all the cases. In the present case debilitating humid temperature continuing over a long period so lowered the patient's resistance that the organism was able to invade the meninges.

3 Benzançon, F, and Lepage. Meningitis Due to *Micrococcus Tetragenus*, *Semaine med* **18** 40, 1898

4 Grieve, J W, Fackler, G A, and Mitchell, E W. Case of *Micrococcus Tetragenus* Meningitis, *Philadelphia M J* **1** 528, 1898

5 Pende, N. Meningitis of *Micrococcus Tetragenus*, *Policlinico (sez prat)* **14** 26, 1907, abstracted, *Centralbl f Bakt* **41** 294, 1908

6 Vincent, M H. Meningitis of *Micrococcus Tetragenus*, *Bull Soc med de Paris* **3** 26, 1908

7 Leschke, E, in Kraus, F, and Brugsch, T. *Spezielle Pathologie und Therapie innerer Krankheiten*, Berlin, Urban & Schwarzenberg, 1919, vol 2, p 1103, cited by Bonanno ⁸ and by Reimann ^{1a}

8 Bonanno, A M. Meningitis Caused by *Gaffkya Tardissima*, abstracted, *Riforma med* **47** 363 (March 9) 1931

With the foregoing statements in mind it will be instructive to examine in detail tables 3 and 4, which compare meningococcic meningitis with that due to *M. tetragenus* and to note how few are the differences in their clinical pictures

TABLE 3—*Comparison of Symptoms, Physical Findings and Complications of Meningitis Due to M. Tetragenus and Meningococcic Meningitis*

Symptoms and Physical Findings	Meningitis Due to <i>M. Tetragenus</i>	Meningococcic Meningitis
Pharyngitis	+	+
Tonsillitis	+	— +
Sinusitis	+	+
Otitis media	— +	+
Fever	+	+
Rapid pulse	+	+
Headache	+	+
Chills	+	+
Vomiting	+	+
Diarrhea	+	+
Constipation	+	+
Pains in the neck	+	+
Backache	+	+
General malaise	+	+
Pains in the joints	+	+
Hyperactive reflexes	+	+
Kernig sign	+ —	+
Brudzinski sign	+ —	+
Hyperesthesia	+	+
Pupillary inequality	+ —	+
Photophobia	+	+
Insomnia	+	+
Delirium	+	+
Coma	+	+
Petechiae	+	+
Herpes	—	+
Epididymitis	—	+
Peritonitis	—	+

TABLE 4—*Comparison of Clinical Pathologic Characteristics of Meningitis Due to M. Tetragenus and Meningococcic Meningitis*

	Meningitis Due to <i>M. Tetragenus</i>	Meningococcic Meningitis
Blood culture	Positive—28%	Positive—5 to 80%
Pressure of spinal fluid	Increased	Not always increased
Cell count of spinal fluid	Increased—number up to 20,000	Increased—number up to 90,000
Globulin content of spinal fluid	Increased—++++	Increased—++++
Sugar content of spinal fluid	Decreased	Decreased
Reaction to colloidal gold test	Typical meningitic curve	0000244444
Differential count (Schilling)	Polynucleosis—many young forms	Polynucleosis—many young forms
Direct smear	Extracellular cocci, some gram positive and some gram negative	Intracellular and extracellular gram negative diplococci
Culture of spinal fluid	Rapid growth on almost all mediums	Slow growth on favor- able mediums

This comparison proves that the proper diagnosis depends almost entirely on the identification of an organism which on direct smear may be atypical and easily confused with the meningococcus or the staphylococcus. Accordingly, cultural studies to bring out the peculiarities of the organism are essential.

BACTERIOLOGY

Dissociation of M. Tetragenus Isolated in the Present Case—Reimann¹ pointed out in 1934 that the *M. tetragenus* which he isolated in a case of meningitis had the tendency to dissociate into three types of colonies, namely, (a) yellow, (b) large and small white and (c) translucent. The yellow colonies produced a large tetrad, the white colonies small cocci, single and in clusters, and the translucent colonies pleomorphic metachromatic cocci. The type found in the translucent colonies was similar to that observed in direct smears from living tissue.

On transfer of the original broth culture to blood agar, the first growth, observed in eighteen hours, consisted of small translucent and white colonies. At the end of forty-eight hours these colonies had differentiated themselves into four types described by Reimann: (a) large yellow colonies with a zone of clear hemolysis, (b) large white colonies with a zone of green hemolysis, (c) small white colonies with a zone of green hemolysis and (d) translucent colonies, occasionally medium sized, with a zone of clear hemolysis.

It was noted that once the dissociation was made on artificial mediums, the characteristics of the colonies remained constant. The yellow colony remained yellow, with the exception that minute white daughter colonies appeared at its margin, the white colony on transfer remained smooth, raised, glistening and white. The small white colony, on transfer to plain agar, remained small for three or four days and then turned slightly cream colored. The translucent colony was noted on the original transfer, but we were unable to recover it, although an occasional colony was noted among other types, which on transfer would not remain constant.

Morphology—The structure of the bacteria composing the different types of colonies was in agreement with the observation made by Reimann. The large yellow colonies were composed of large, deep-staining, gram-positive tetrads and showed the typical tetrad formation.

The large white colonies were composed of deep-staining, all gram-positive cocci and diplococci, small and with no tetrad formation. There was a suggestion of bipolar arrangement. These colonies would have been difficult to distinguish from staphylococci.

The small white colonies were composed of gram-positive and gram-negative cocci. Their structure was as indefinite as their Gram staining.

There were globular forms, diplococcic and coccic forms and meta-chromatic chained cocci

The translucent colonies, in our short observation of this type of growth were made up of the same pleomorphic type of cocci

Cultural Characteristics on Broth Mediums—The yellow colony retained its color in broth mediums. The pellicle was yellow and more prolific than that formed by the other colonies. In 500 cc of beef

TABLE 5—*Cultural Characteristics of M. Tetragenus**

Type of Colony on Agar Plate	Structure of Cocci	Growth on Broth	Growth on Gelatin	Growth on Blood Plate	Dextrose	Lactose	Mannite	Xylose	Maltose	Sucrose	Dulcitol
Yellow colony, elevated, lobate edges	Micrococci large, gram positive, dividing in two planes	Yellow pellicle dropping to form weedy sediment	No liquefaction	Yellow colony with clear zone of hemolysis	+ 3d day	—	—	—	+ 3d day	—	—
White colony, large, smooth elevated, dome shaped	Cocci and diplococci, all gram positive, smaller, with no tetrads	White pellicle later forming weedy glutinous sediment	Slow liquefaction of gelatin	White colony with green zone of hemolysis	+ 1st day	+	—	—	+ 1st day	+ 2d day	—
White colony, small, convex	Gram positive and gram-negative cocci and diplococci with globular forms	White pellicle with granular sediment	Slow liquefaction of surface	Early clear hemolysis, later green	+ 1st day	—	—	—	+ 1st day	—	—
Translucent colony, flat, clear, large and small	Same as small white colony	Fragile pellicle with clear underlying liquid, later drops		Clear zone of hemolysis	Not done						
Whitish colony, glutinous, difficult to emulsify	Gram positive, spherical, dividing in two planes, with tetrads	Superficial liquid, clear weedy spiraling deposits			+ + — — + + — High pathogenicity for mouse						

* Acetic acid odor for yellow and white colonies

infusion broth this pellicle would form completely in three days and disintegrate on the fourth day. In addition to the yellow color, there was a greenish discoloration, which is characteristic of the proteose peptone mediums.

Cultures of the large and of the small white colonies were similar on broth mediums, in that they maintained their white color in broth, formed a pellicle and on its disintegration formed the same glutinous thready sediment.

The yellow colonies did not liquefy gelatin, but the large and small white colonies did. This was one of the few means of differentiating the organism from the staphylococcus.

Sugar Reactions—The yellow colonies did not form acid on dextrose and maltose until the third day, while the large and small white colonies formed acid within twenty-four hours. The large white colonies did not ferment sucrose until the second day or lactose until the third.

For all cultures a distinct odor was noted, not unlike that of vinegar or acetic acid.

Pathogenicity for Animals—An agar slant culture of each of the three types of colony, suspended in saline solution, was inoculated intravenously into a rabbit and a guinea pig. This was done to determine if one type of colony was more virulent or produced more toxin than the other. There was no pathogenic effect whatsoever from these inoculations. None of these types killed mice.

Immunity—The patient was given polyvalent antimeningococcus serum throughout the course of the disease and recovered.

TABLE 6—*Agglutination Tests of Three of M. Tetragenus Types of Colony Against Gordon's Four Types of Antimeningococcus Serum*

Type of Colony	Gordon's Four Types of Antimeningococcus Serum			
	Type 1	Type 2	Type 3	Type 4
Yellow colony	1:10	1:80	1:20	1:20
Large white colony	Negative	Negative	Negative	Negative
Small white colony	Negative	Negative	Negative	Negative

Early in the disease it was found that *M. tetragenus* was agglutinated by polyvalent antimeningococcus serum with dilutions as high as 1:160. Therefore, further agglutination tests were carried out against the four types of meningococcus to determine if this organism held any relation to Gordon's four types.

From the results of the agglutination tests as seen in table 6, it would appear that, serologically, the yellow colony was most nearly related to the meningococcus. Therefore, if the production of an antiserum for this infection is to be considered, the yellow colony would probably be of the greatest value as an antigen. The serum of the patient during the disease and after recovery did not agglutinate the meningococcus or any of the three types of colony of *M. tetragenus*.

SUMMARY

A case of meningitis due to *M. tetragenus* has been reported.

The clinical features, symptoms and laboratory findings were similar to those of meningococcic meningitis. The only differential point was the identification of an organism, atypical in the original smears, but becoming typical of *M. tetragenus* tetrads in broth cultures.

Microbic dissociation was found. The yellow colony was the undissociated type. It formed daughter white colonies which differentiated into large and small white colonies. The typical structure of the organism was found in the large yellow colonies in the form of tetrads. The large white colonies furnished only cocci and diplococci, which were difficult to distinguish from staphylococci. The small white colony was still further dissociated, in that no tetrads were seen, and the form of the cocci was indeterminate.

A table presenting the cultural characteristics of the three types of colony has been presented. It was found that, once dissociated, each type of colony on transfer to various types of medium maintained its characteristics.

Agglutination tests—the three types of colony against the patient's own serum and Gordon's four types of antimeningococcus serum—were carried out. The yellow colony was not agglutinated by the patient's own serum but was agglutinated by antimeningococcus serum, type 2, with a dilution of 1:80.

The three types of colony were cultured individually in 500 cc of proteose hormone broth and within four days filtered through a Pasteur-Chamberland filter. The filtrates were tested on three types of animal, rabbit, guinea pig and mouse. Cutaneous tests were made with the filtrates in strength varying from 1:100,000 dilution to full strength on 10 persons.

CONCLUSIONS

1 It has been observed that *M. tetragenus* is not the harmless organism commonly supposed but under certain circumstances is pathogenic.

2 It occurs as an etiologic agent much more frequently than is recognized, usually being mistaken for a meningococcus or a staphylococcus.

3 Its characteristics of dissociation should be recognized in order to establish its identity.

4 It elaborates a soluble toxin which produces a reaction in the skin of human beings but is not demonstrably toxic for animals.

EXPERIMENTAL PRODUCTION OF NEUTROPENIA WITH AMINOPYRINE

E M BUTT, M D

A M HOFFMAN, M D

AND

S N SOLL, M D

LOS ANGELES

The reproduction of the classic clinical picture of malignant neutropenia, or agranulocytic angina, in experimental animals has never been accomplished successfully. The situation in regard to aminopyrine as the most common etiologic agent in agranulocytic angina in man is much the same today as that in regard to cinchophen as the cause of acute necrosis of the liver. Cinchophen is generally accepted as the toxic agent in production of acute yellow atrophy in certain susceptible persons. In the experimental animal, however, cinchophen has never produced necrosis of the liver in any degree sufficient to simulate the condition in man. Aminopyrine today is accepted by many as the responsible agent in agranulocytic angina. True, it is apparently harmless to the vast majority of patients. Rawls¹ estimated on clinical grounds that only 1 to 2 per cent of patients are susceptible to demonstrable changes in the peripheral blood, this view is based on an "individual susceptibility." If the same numerical proportion exists in animals, it is understandable that the experimental reproduction of the disease would be difficult, if only because of the large number of animals required. It is our belief on the basis of our efforts during the past three years to reproduce the disease with aminopyrine in animals that the toxic action of the drug is far more frequent than Rawls' figures would indicate. We believe that changes in the bone marrow occur in the majority of animals but that changes in the peripheral blood are seen in only a small proportion.

Attempts at experimental reproduction of neutropenia have been numerous. In 1932, before the attention of workers was focused on

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1 Rawls, W B. Effect of Amidopyrin on Red, White, and Polymorphonuclear Blood Cells of a Series of One Hundred Patients, *Am J M Sc* **192** 175 (Aug) 1936

aminopyrine, Kracke² reported successful reproduction of agranulocytosis in rabbits with small subcutaneous or intraperitoneal doses of benzene. Large doses administered by the same technic affected the erythroblastic elements as well. Intravenous injection of benzene killed the rabbits immediately. Marked leukopenia was produced by the subcutaneous injection of salicylic acid and by intravenous administration of hydroquinone. Oral, subcutaneous or intravenous use of aminopyrine, acetophenetidin, aminopyrine diethylbarbiturate, dial, resorcinol, pyrocatechin, orthocresol, metacresol, paracresol, phenol, paraoxybenzoic acid, metaoxybenzoic acid and 50 per cent alcohol failed to affect the leukocyte count.

Fried and Dameshek,³ in 1932, infected rabbits intravenously with *Salmonella supestifer* and caused temporary neutropenia. Kracke⁴ justly pointed out that such temporary neutropenia can be produced "by a wide variety of substances, including milk, nonspecific proteins, dead and living bacteria and various types of inert, finely divided material" and that such temporary neutropenia in no way simulates true agranulocytosis.

Dennis⁵ placed cultures of *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Streptococcus viridans* and *Proteus septicus* in parchment capsules, inserted the capsules into the abdominal cavities of rabbits and observed what he interpreted as granulopenia. Most of the rabbits showed no drop, but rather a rise, in the total leukocyte count, while some showed a moderate to marked decrease in the polymorphonuclear count.

Meyer and Thewlis⁶ were unable to obtain results similar to those of Dennis. With *Bacillus pyocyaneus*, however, they produced leukopenia in rabbits, with death in forty hours but with no decrease in the number of polymorphonuclear cells. Ricci⁷ inoculated rats with living cultures of *S. supestifer* and *B. pyocyaneus* and produced varying degrees of

2 Kracke, R. R. The Experimental Production of Agranulocytosis, *Am J Clin Path* **2**:11 (Jan) 1932.

3 Fried, B. M., and Dameshek, W. Experimental Agranulocytosis. Infections of Rabbits with *Salmonella Supestifer* by Way of the Blood Stream, *Arch Int Med* **49**:94 (Jan) 1932.

4 Kracke, R. R. "Experimental Agranulocytosis," *Arch Int Med* **49** 709 (April) 1932.

5 Dennis, E. W. Experimental Granulopenia Due to Bacterial Toxins Elaborated in Vivo, *J Exper Med* **57**:993 (June) 1933.

6 Meyer, O. O., and Thewlis, E. W. A Report of Failure to Produce Granulocytopenia with Bacterial Toxins, *J Clin Investigation* **13**:437 (May) 1934.

7 Ricci, F. C. Sulla agranulocitosi sperimentale, *Arch ital di otol* **46**:401 (June) 1934.

leukopenia and agranulocytosis In his animals, however, abscesses in the liver developed Harris and Schattenberg⁸ claimed that by injecting prepared toxins of *Bacillus enteritidis* and *Str. haemolyticus* into guinea pigs they had reproduced the blood picture found in human beings *Staph. aureus* from a patient who had died of the disease brought about depression of the total leukocyte count and neutropenia in guinea pigs but not in rabbits

De Vries'⁹ first indication, in September 1933, of the possible relation of aminopyrine to granulopenia in human beings, followed by the reports of Madison and Squier,¹⁰ Watkins,¹¹ Hoffman, Butt and Hickey,¹² Randall¹³ and many others, gave a great impetus to the experimental study of the disease, which was now centered about aminopyrine as the etiologic agent The majority of the authors reported satisfactory results Strangely enough, the earliest of their observations may be one of the most significant In a short note, Miller¹⁴ reported results of oral administration of 0.3 Gm. of a 5 per cent solution of aminopyrine per kilogram of body weight to 16 dogs It was given for four weeks, and no instance of depression of the total number of circulating leukocytes was encountered

Histological study of the femoral bone marrows of the treated animals, however, revealed striking changes, which gave evidence that the drug does affect the formation of granulocytes, even though not to a degree which is reflected in a materially decreased number of granular leukocytes in the circulating blood A well-defined suppression of maturation of the hematopoietic elements occurs

8 Harris, W. H., and Schattenberg, H. J. Experimental Studies in So-Called Agranulocytic Angina. I. Effects upon Leucocytes by Toxic Products of Bacteria from Stool of Human Case, *Proc. Soc. Exper. Biol. & Med.* **31** 843 (April) 1934. Schattenberg, H. J., and Harris, W. H. II. Effects upon Leucocytes by Toxic Products of *Staphylococcus Aureus* from Blood of Human Case, *ibid.* **31** 847 (April) 1934.

9 de Vries, S. I., Jr. Recurrent Agranulocytic Syndrome, *Nederl. tijdschr. v. geneesk.* **77** 4443 (Sept. 30) 1933.

10 Madison, F. W., and Squier, T. L. (a) Primary Granulocytopenia After Administration of Benzene Chain Derivatives, *J. A. M. A.* **101** 2076 (Dec. 23) 1933, (b) The Etiology of Primary Granulocytopenia, *ibid.* **102** 755 (March 10) 1934.

11 Watkins, C. H. The Possible Role of Barbiturates and Amidopyrine in the Causation of Leucopenic States, *Proc. Staff Meet., Mayo Clin.* **8** 713 (Nov. 22) 1933.

12 Hoffman, A. M., Butt, E. M., and Hickey, N. G. Neutropenia Following Amidopyrine, *J. A. M. A.* **102** 1213 (April 14) 1934.

13 Randall, C. L. Severe Granulopenia Following the Use of Barbiturates and Amidopyrine. Report of a Case, *J. A. M. A.* **102** 1137 (April 7) 1934.

14 Miller, D. K. Histological Changes in the Bone Marrow of the Dog Following Amidopyrine Administration, *Science* **80** 320 (Oct. 5) 1934.

Granulocytes are decreased in numbers or almost completely absent. The number of young, relatively undifferentiated cells is increased. Many erythroblasts and myeloblasts are present, as are cells of an even more primitive type, more adult forms are rare. In certain more advanced cases the orderly arrangement of the bone marrow structure into hematopoietic islands has been disturbed.

From the observations reported it appears that amidopyrine orally administered may exert a toxic effect upon the bone marrow, with little or no evidence of the fact in the circulating granular elements of the blood.

These observations are consistent with those on human bone marrow in fatal cases reported by Fitz-Hugh and Krumbhaar¹⁵ in a paper in which they proposed the hypothesis of "maturation arrest." Custer¹⁶ reported observations which he made on human bone marrow in 11 cases, using marrow from the tibial and femoral shafts as an example of that from the long bones and marrow from the vertebrae, sternum or ribs as an example of that from cancellous bone. He pointed out that an examination based on marrow removed from but one locus is "woefully inadequate." In 9 of the 11 cases of proved idiopathic agranulocytosis he observed

- (a) *Marked proliferation of myeloblasts*
- (b) Failure of these cells to mature, resulting in paucity of myelocytes and practically complete absence of segmented forms
- (c) Normal or slightly increased formation of red blood cells
- (d) Slight hyperplasia of otherwise normal megakaryocytes
- (e) Infiltration of lymphocytes and plasmocytes

The careful observations both of Fitz-Hugh and Krumbhaar and of Custer were amply confirmed by Darling, Parker and Jackson¹⁷ in a study of the bone marrow of 24 persons who died and of the sternal bone marrow of 1 patient who recovered. They suggested the term "granulocytic anaknesis" for the type of arrest of maturation observed in the bone marrow in agranulocytic angina.

Madison and Squier,^{10b} in their clinical report, described their attempts to produce agranulocytosis in rabbits. Eleven rabbits received allonal (allylisopropylbarbituric acid with aminopyrine) by mouth in doses of $2\frac{2}{3}$ to 24 grains (0.17 to 1.55 Gm) daily. One rabbit which had received an average of 20 grains (1.29 Gm) daily

showed a rather abrupt drop in both the total and the granulocyte count on the twenty-fifth day, following which there was a progressive fall until death on

15 Fitz-Hugh, T, Jr, and Krumbhaar, E B. Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, *Am J M Sc* **183** 104 (Jan) 1932

16 Custer, R P. Studies on the Structure and Function of the Bone Marrow IV. Bone Marrow in Agranulocytosis, *Am J M Sc* **189** 507 (April) 1935

17 Darling, R C, Parker, F, and Jackson, H. The Pathological Changes in the Bone Marrow in Agranulocytosis, *Am J Path* **12** 1 (Jan) 1936

the thirtieth day Preceding death there was complete absence of granulocytes in the peripheral blood and the blood picture was characteristic of primary granulocytopenia except for a moderate anemia. At necropsy there were no grossly abnormal conditions found save that the bone marrow was absolutely lacking in cells of the granular series. None of the other rabbits showed the blood picture of granulocytopenia.

No mention was made, however, of observations on the bone marrow of these rabbits.

In our early report¹² we described our results with oral administration of aminopyrine to rabbits in doses of 0.2 to 0.9 Gm per kilogram. Definite leukocytosis was produced in all the animals, followed in a few weeks by a depression of the total white cell count. In all the rabbits the polymorphonuclear leukocyte count was reduced to 20 per cent, while a few animals showed depression to as low as 8 per cent. However, because of the known wide normal variation of the leukocyte counts of rabbits, we felt that these results were not conclusive and therefore limited further experimental study to dogs.

Stenn¹⁸ reported observations on the effect of aminopyrine on 120 animals, including the guinea pig, rabbit and monkey, over a period of eight months and concluded "Administration of amidopyrine both with and without preliminary anemia or bone marrow injury, failed to produce any appreciable granulocytopenia." No observations on the bone marrow were recorded.

Climenko¹⁹ observed that after oral administration of aminopyrine to rabbits—without depression of granulocytes in the circulating blood—the leukocytosis which usually follows injection of nucleic acid intramuscularly failed to occur. The bone marrow of the experimental animals showed marked hyperplasia, with an increase in the number of primitive hemocytoblasts. Essentially the same type of inhibition of the bone marrow preceded by an increase in the percentage of juvenile forms without concomitant leukocytosis was produced after administration of α -dinitrophenol. The first case of agranulocytic angina due to α -dinitrophenol in man was reported in our original paper.¹²

Kunde, Herwick, Learner and Sternback²⁰ administered a preparation of aminopyrine and dial (cibalgin) to 35 rabbits with endemic

18 Stenn, F. Etiologic Relationship of Amidopyrine to Agranulocytosis, *J Lab & Clin Med* **20** 1150 (Aug.) 1935.

19 Climenko, D. R. Inhibition of Leucogenic Activity in the Rabbit by Certain Cyclic Compounds, *Proc Soc Exper Biol & Med* **32** 823 (March) 1935.

20 Kunde, M. M., Herwick, R. P., Learner, A., and Sternback, M. Non-Production of Granulocytopenia with an Amidopyrine Compound in Some Acute Infections, *Proc Soc Exper Biol & Med* **32** 1121 (April) 1935.

laboratory infections, such as snuffles and acute gastrointestinal disorders. They concluded that the drug did not diminish the number of leukocytes in normal rabbits when given for seventeen days and observed no depression of the leukocytosis present in the infected animals. Thyroidectomized animals showed the same results as the others. No observations on the bone marrow are recorded.

Bolton²¹ administered 0.3 Gm of aminopyrine in water by stomach tube to a dog over a period of twenty-three days. The leukocyte count remained elevated from 18,000 to 20,000, with no significant change in the differential count. Sections from the femur, humerus and ribs showed "hyperplasia of the bone marrow, with no decrease in the myeloid elements." In another dog (experiment 11) larger doses of aminopyrine were followed by depression of the original leukocyte count of 12,200 to 6,500. There was a subsequent rise to the original level, with no change in the percentage of granulocytes. Additional doses were given intravenously—altogether, 4.5 Gm of the drug for each kilogram of body weight over a period of thirty-three days. No necropsy was reported.

Smith and Mack²² studied the effect of amytal and aminopyrine given orally to albino rats fed a deficient diet. They concluded that the total white cell count could be reduced approximately 50 per cent in the animals weakened by the deficient diet, but they did not note any change in granulocytes or any abnormality in the bone marrow.

Wilson²³ administered phenobarbital and aminopyrine subcutaneously, both in combination and separately, to white rats for twenty-eight days and noted only leukocytosis. A few normoblasts were found in the aminopyrine series, and he concluded that the bone marrow was affected in some manner. The bone marrow was not studied.

Miller and Rhoades²⁴ reported further work on the effect of a deficient diet combined with aminopyrine on dogs. Dogs fed 0.5 Gm

21 Bolton, V. L. Laboratory Study of Amidopyrine, Barbitol, Phenyl Hydrazine, and Benzene in Relation to Agranulocytic Angina, *J. Lab. & Clin. Med.* **20** 1199 (Aug.) 1935.

22 Smith, E., and Mack, L. Effect of a Deficient Diet, Amytal and Amidopyrine on the Blood Picture of the Albino Rat, *Proc. Soc. Exper. Biol. & Med.* **32** 1623 (June) 1935.

23 Wilson, S. J. Effects of Amidopyrine and Phenobarbital on the Blood Cell Count of White Rats, *J. Kansas M. Soc.* **36** 500 (Dec.) 1935.

24 Rhoades, C. P., and Miller, D. K. Effect of Diet on the Susceptibility of the Canine Hematopoietic System to Damage by Amidopyrine, *Proc. Soc. Exper. Biol. & Med.* **36** 654 (June) 1937. Miller, D. K., and Rhoades, C. P. Effect of Diet on the Susceptibility of the Canine Hematopoietic Function to Damage by Amidopyrine, *J. Exper. Med.* **66** 367 (Sept.) 1937.

of aminopyrine daily failed to demonstrate a change in the blood picture. They further found that in dogs receiving the Goldberger pellagra-producing (blacktongue) diet appreciable anemia usually failed to develop. The combination of the drug and the diet, however, produced pronounced and often fatal anemia in from eight to thirty-five days. There was remarkable absence of leukopenia. The bone marrow histologically resembled that described in cases of benzene poisoning.

Numerous experimental observations on man have been recorded. Benjamin and Biederman,²⁵ Kloster,²⁶ Hansen and Holten,²⁷ Plum²⁸ and Dameshek and Colmes²⁹ have each reported on from 1 to several patients with known susceptibility to aminopyrine who had granulopenia again when aminopyrine was administered after recovery from the original attack. Hourly counts were frequently significantly altered immediately after ingestion of the drug. Most of the patients so tested gave negative responses to aminopyrine in intradermal scratch, passive transfer and patch tests. Dameshek and Colmes, however, attempted intradermal tests with blood serum previously "sensitized" by aminopyrine. These gave positive results in the 3 cases in which they were tried.

EXPERIMENTS

Aminopyrine (dimethylaminoantipyrine) was fed to a group of 7 dogs. An eighth, dog 5 in the series, was kept as a control. The drug was administered to dogs 1, 2 and 3 through a stomach tube. Dogs 4, 6, 7 and 8 in a second series of experiments were fed gelatin capsules containing the powdered drug.

The initial dose of aminopyrine fed to dogs 1, 2 and 3 was approximately 0.5 Gm per kilogram. Ten minutes after the administration dog 2 died in convulsions. Dogs 1 and 3 vomited a portion of the drug and several days later had completely recovered from the toxic effects of the initial dose. The dose of aminopyrine

25 Benjamin, J. E., and Biederman, J. B. Agranulocytic Leukopenia. Report of a Case Successfully Treated with X-Rays and Some Observations on the Effect of Amidopyrine, *J. A. M. A.* **103** 161 (July 21) 1934.

26 Kloster, J. A Case of Granulocytopenia Produced Experimentally by Pyramidon "Bayer," *Acta med. Scandinav.*, 1936, supp 78, p. 595.

27 Hansen, A. B., and Holten, C. Hypersensitiveness to Amidopyrin with Resulting Granulopenic Reaction, *Acta med. Scandinav.*, 1936, supp 78, p. 599.

28 Plum, P. Studies on the Etiological Significance of Amidopyrin (Pyramidon) in Agranulocytosis, *Acta med. Scandinav.*, 1936, supp 78, p. 605, Effect of Amidopyrine on Granulocytopoiesis of Bone Marrow. Continued Investigations on the Etiology of Agranulocytosis, Preliminary Report, *Ugeskr. f. læger* **98** 91 (Jan 30) 1936.

29 Dameshek, W., and Colmes, A. Effect of Drugs in the Production of Agranulocytosis with Particular Reference to Amidopyrine Hypersensitivity, *J. Clin. Investigation* **15** 85 (Jan) 1936.

was then reduced to 0.05 Gm per kilogram and was gradually increased to approximately 0.35 Gm per kilogram. Dog 3 lived for seven months, receiving a total of 136.4 Gm of the drug, administered in sixty-four doses. On two occasions convulsions developed in this animal and were successfully treated with barbitol and caffeine with sodium benzoate. Dog 1 survived for ten months, receiving a total of 250.9 Gm of aminopyrine, in one hundred and twenty-three doses.

The leukocyte count for dog 3 varied from 8,500 to 12,000. On two occasions leukocytosis (14,500 and 15,500 cells) was noted. The white cell count did not

TABLE 1—*Details of Experiments on 8 Dogs*

Dog No	Dose of Aminopyrine, Gm /Kg			Total Administration		Variation in Blood Count		Changes in the Bone Marrow	Duration of Experiment, Mo	Comment
	Initial	Low est	High-est	Gm	No of Doses	Leuko cytes	Erythro cytes			
1	0.52 (Very ill)	0.055	0.28	250.9	123	45,000 to 350	9,130,000 to 4,900,000	Marked aplasia	10½	Died during stage of marked granulopenia
2	0.54									Died 10 minutes after administration
3	0.53 (Vomited some of drug)	0.058	0.35	136.4	64	15,000 to 6,000	9,100,000 to 3,500,000	Moderate aplasia	6½	Comatose for 12 hr, died of air embolism
4	0.12		0.12	2.0	2					Sick at beginning of experiment
5	Control dog					8,000 to 12,000	Count not made	None	10½	
6	0.06	0.06	0.22	26.75	29	14,000 to 6,000	6,300,000	Slight aplasia	2½	Found dead in cage
7	0.027	0.027	0.21	255.5	167	22,000 to 6,000 (No counts 5 days before death)	7,400,000 to 5,200,000	Marked aplasia	9	Found dead in cage
8	0.036	0.036	0.21	60.2	65	17,500 to 5,500		Slight aplasia	4	Died while passing stomach tube

fall below 6,000. The percentage of polymorphonuclear leukocytes varied from 52 to 80. The red cell count was 9,100,000 at the beginning of the observations and 6,400,000 at the end of the experiment. The platelets were not counted but appeared numerous in all slides.

The white cell count of dog 1 dropped to 900 at the end of the fifth month. The dose of aminopyrine was reduced from 0.28 to 0.14 Gm per kilogram, and two days later the white cell count increased to 32,000, of which 95 per cent were polymorphonuclear cells. The dose of aminopyrine was then gradually increased to 0.33 Gm per kilogram, but later it was dropped to 0.25 Gm per kilogram, as the former dose was too toxic. The day before the death of the animal the white blood cell count was 350. No polymorphonuclear leukocytes were found in the blood smears.

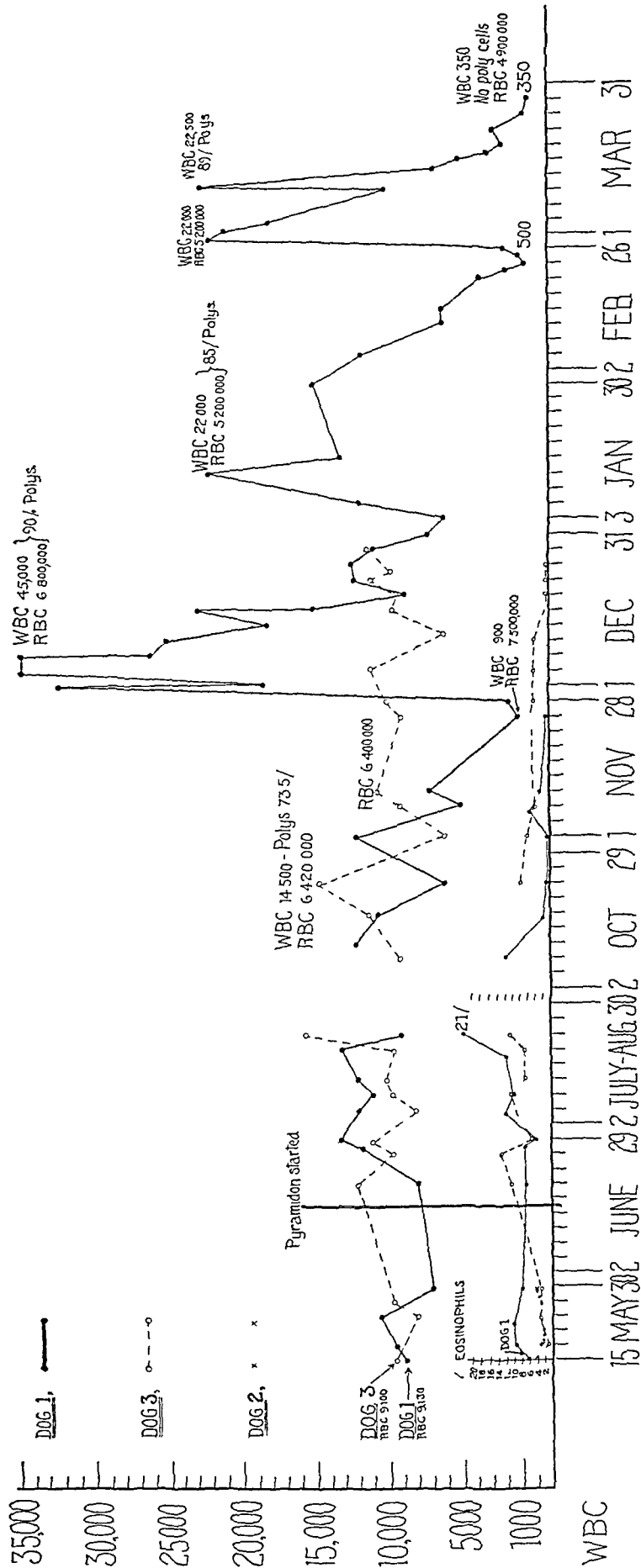


Fig 1 —Details of experiments on dogs 1, 2 and 3

Dog No	Weight During Experiment, kg		Gm of Aminopyrine per kg of Body Weight		Total Drug Given, Gm	Total Number of Doses	Comment
	Beginning	End	Initial Dose	Reduced to			
1	9	5.75	0.52	0.055	250.9	123	Death in 10 minutes Vomited until dose
2	8.5	7.2	0.54	0.058	0.54	1	
3	8.5	7.2	0.53	0.058	136.4	64	
6	9.2	6.8	0.06	0.027	26.75	29	
7	9.2	6.8	0.06	0.027	255.5	167	
8	9.2	6.8	0.06	0.027	60.2	65	

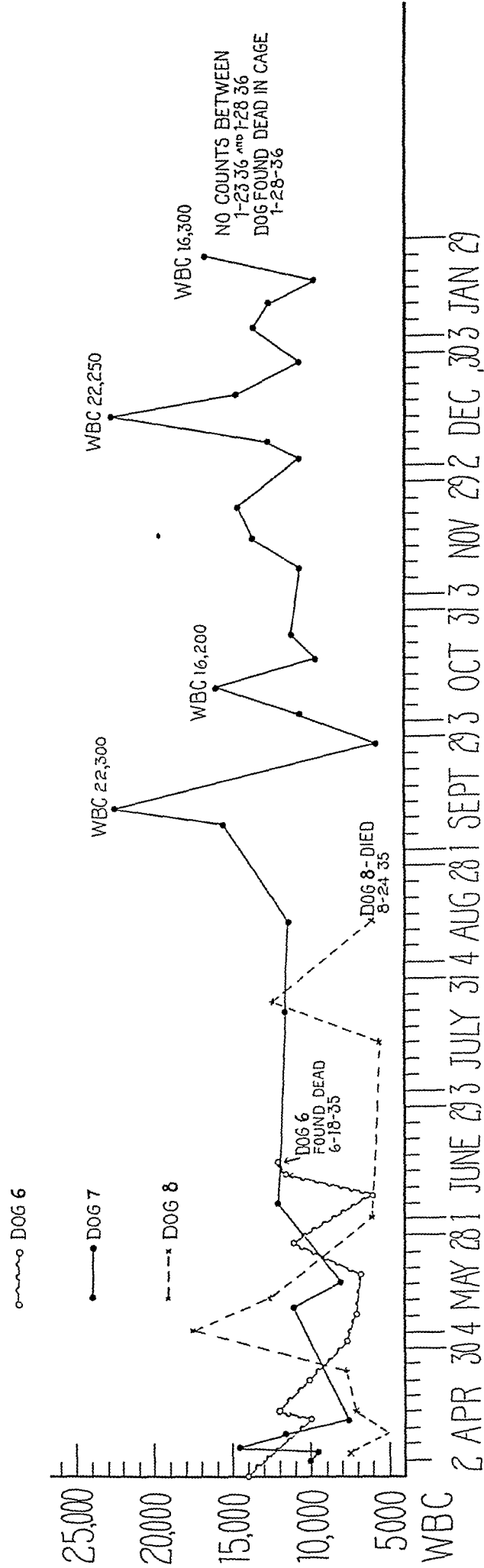


Fig 2 —Details of experiments on dogs 6, 7 and 8

Some details of the blood counts of dogs 1 and 3 are recorded in table 2. Other details of the experiments appear in figure 1 and table 1.

Dog 4 died of a pulmonary infection shortly after the beginning of the experiment. Details of the experiments conducted with dogs 6, 7 and 8 are found in figure 2 and table 1. Dog 7 was the only one of this series to survive any great

TABLE 2—*Details of Blood Counts of Dogs 1 and 3*

			Polymorpho nuclear				
	Erythro cyte Count	Leuko cyte Count	Neutrophilic Leukocytes, %	Lympho cytes, %	Mono cytes, %	Eosino phils, %	Baso phils, %
Dog 1							
5/15/34	9,130,000	8,900	56	33	5	6	
5/18/34	7,610,000	9,700	62	23	5	10	
5/23/34	9,440,000	10,400	60	24	6	10	
5/29/34	9,200,000	7,200	53	36	3	8	
6/20/34	9,760,000	8,000	62	24	7	7	
	(Administration of aminopyrine started)						
6/27/34	7,930,000	11,500	59	30	4	7	
7/20/34	8,160,000	9,100	59	14	6	21	
10/23/34	11,000,000	5,600	49	31	18	2	
11/ 6/34	7,300,000	5,000	60	32	4	4	
11/26/34	7,500,000	900	2	93	5		
11/27/34	6,800,000	1,250	1	94	5		
12/ 3/34		45,000	90	5	5		
12/20/34	4,820,000	8,300	84	5.5	10.5		
1/29/35		14,700					
2/11/35		6,000	69	22	9		
2/25/35		800	18	76	6		
2/28/35		22,000	54	30	16		
3/16/35		5,000					
3/25/35		400	16	72	12		
3/27/35		350	0	98	2		
3/28/35	Died						
Dog 3							
5/15/34	9,100,000	9,700	69	23	3	5	
5/18/34	8,200,000	9,150	63	29	2	1	
5/23/34	8,790,000	8,000	73	17	7	3	
5/29/34	7,840,000	9,800	51	40	6	3	
	(Administration of aminopyrine started)						
6/27/34	7,380,000	9,800	54	31	2	13	
7/ 4/34	6,060,000	7,700	62	21	8	9	
7/20/34	6,530,000	15,500	63	17	4	11	
11/ 1/34		6,200	68	17	8	6	1
12/12/34		6,000	81	11	7	1	
12/24/34	3,500,000	9,400	74	18	7		
12/30/34	Died						

length of time. Unfortunately, no white blood cell counts were made on this dog for five days preceding death. It is probable that the white cell count was low, as the bone marrow was fully as aplastic as that found in dog 1.

The presentation of the main details of the observations at autopsy is limited to animals 1, 3, 7 and 8, as the few changes noted in the remainder of the dogs are not relevant to the problem. None of the dogs had gangrenous or ulcerative lesions of the gastrointestinal tract. Grossly the various organs, except the bone marrow, appeared normal. Microscopically the spleens contained considerable

amounts of coarsely granular, iron-containing pigment Erythroblasts were observed in the spleens of dogs 1 and 7, and the lymphoid tissue was scanty

The bone marrow of dogs 3 and 8 could not be distinguished grossly from normal marrow, except perhaps for some increase in red marrow The bone marrow of dogs 1 and 7 was interesting in that nearly all the marrow was thin

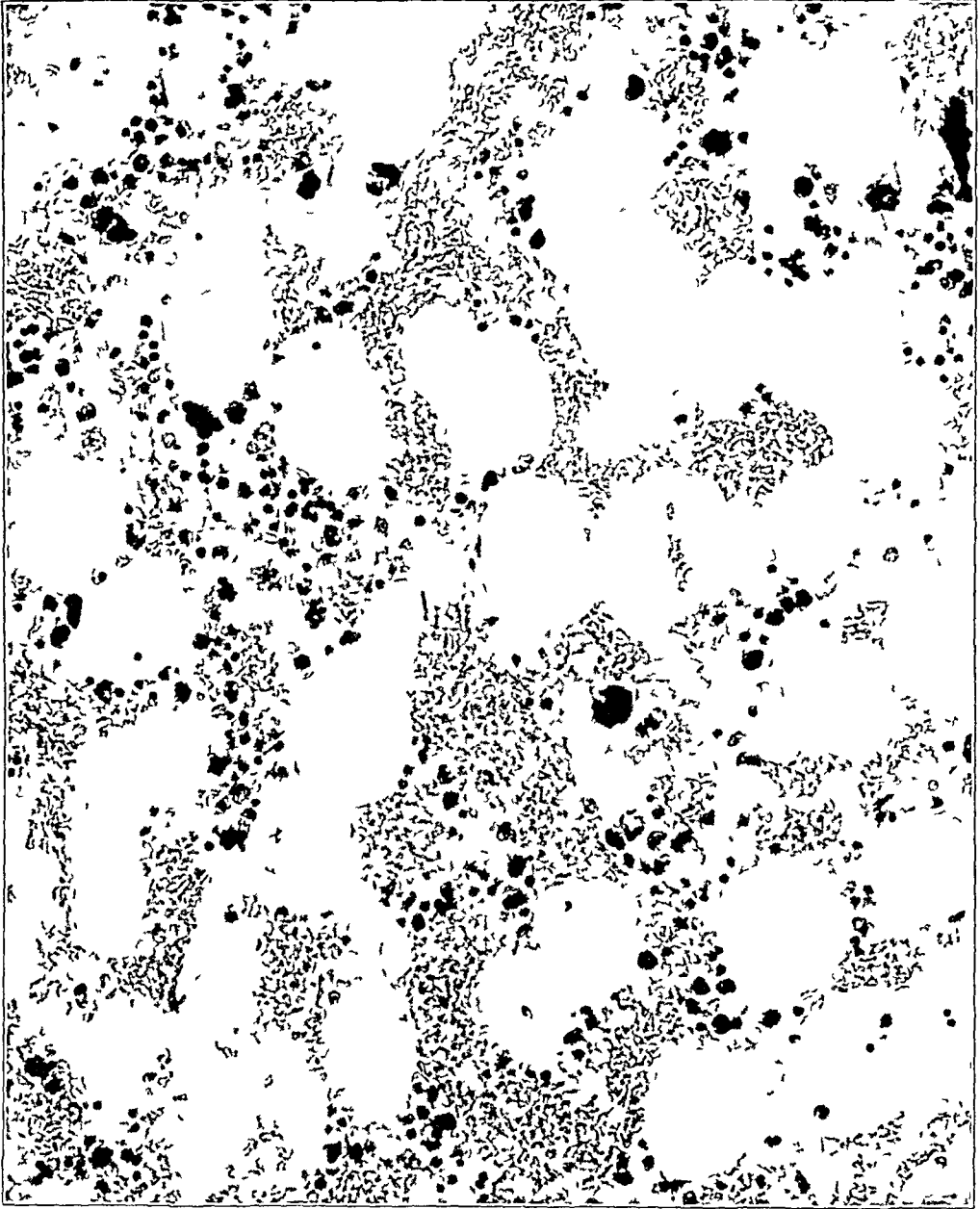


Fig 3 (dog 1) —Bone marrow of the humerus ($\times 310$)

and red and contained streaks of fat Histologic examination revealed nearly complete aplasia of the myeloid elements of the marrow There was noticeable aplasia of the erythroblastic cells Between the small islands of bone marrow tissue were dilated vascular channels filled with red blood cells and fatty tissue The megakaryocytes appeared to be reduced in number

Microscopically the marrow of dog 3 presented moderate but definite aplasia of the myeloid cells, with relative increase of the erythroblastic cells. Minor changes in the marrow were noted in dogs 6 and 8, which could be interpreted as slight hyperplasia or slight aplasia of the myeloid cells, depending on the location of the marrow.

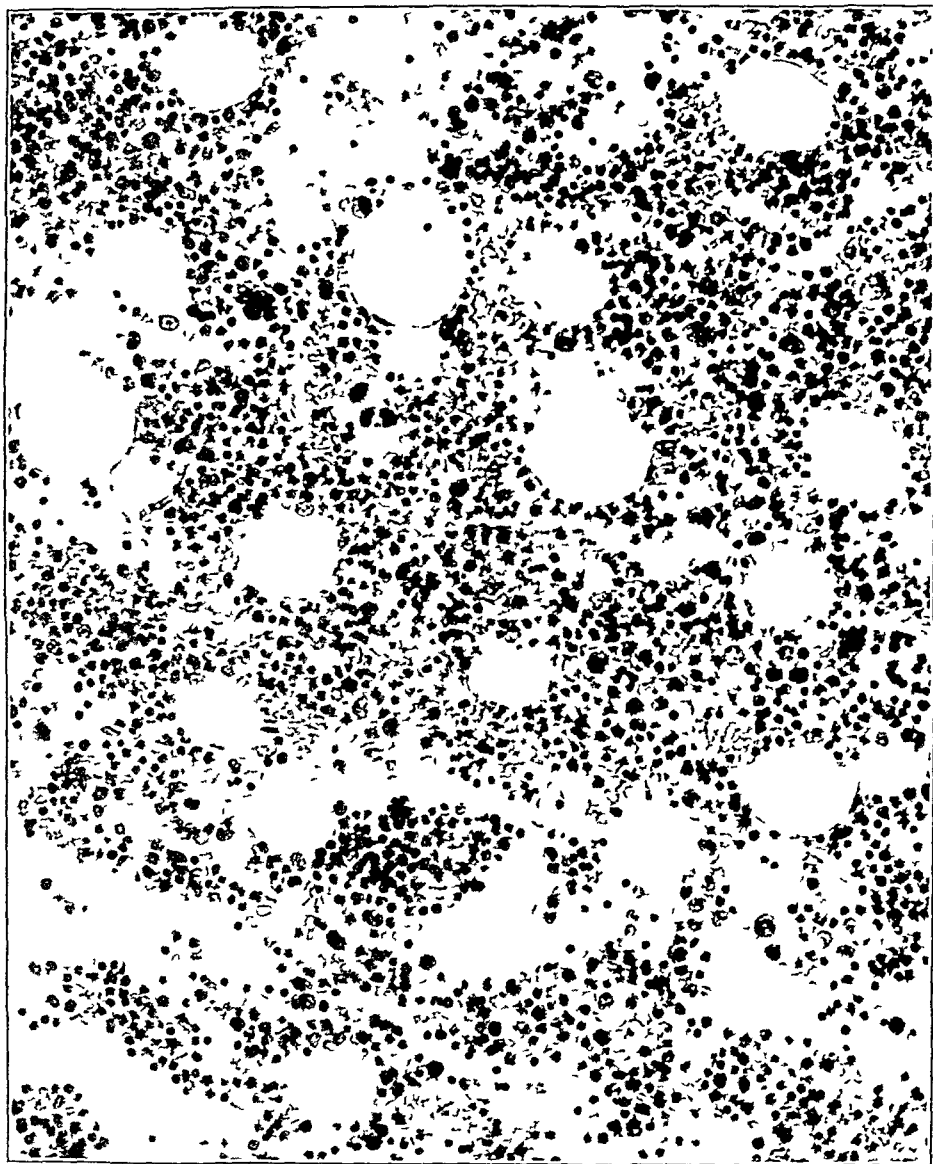


Fig 4 (dog 3) —Bone marrow of the humerus ($\times 310$)

An interesting relation between the total number of grams of aminopyrine administered and the degree of aplasia of the bone marrow is noted in table 1. The most marked aplasia of the bone marrow was observed in the 3 dogs receiving the largest amounts of aminopyrine. Three of the remaining dogs died of the systemic toxic effects of the drug before changes in the bone marrow were sufficiently marked to be unequivocal.

In the foregoing account it has been clearly demonstrated that aplasia of the bone marrow of dogs follows the oral administration of large quantities of aminopyrine. The action is not unlike that of benzene and is somewhat selective, as the destruction of myeloid elements pre-

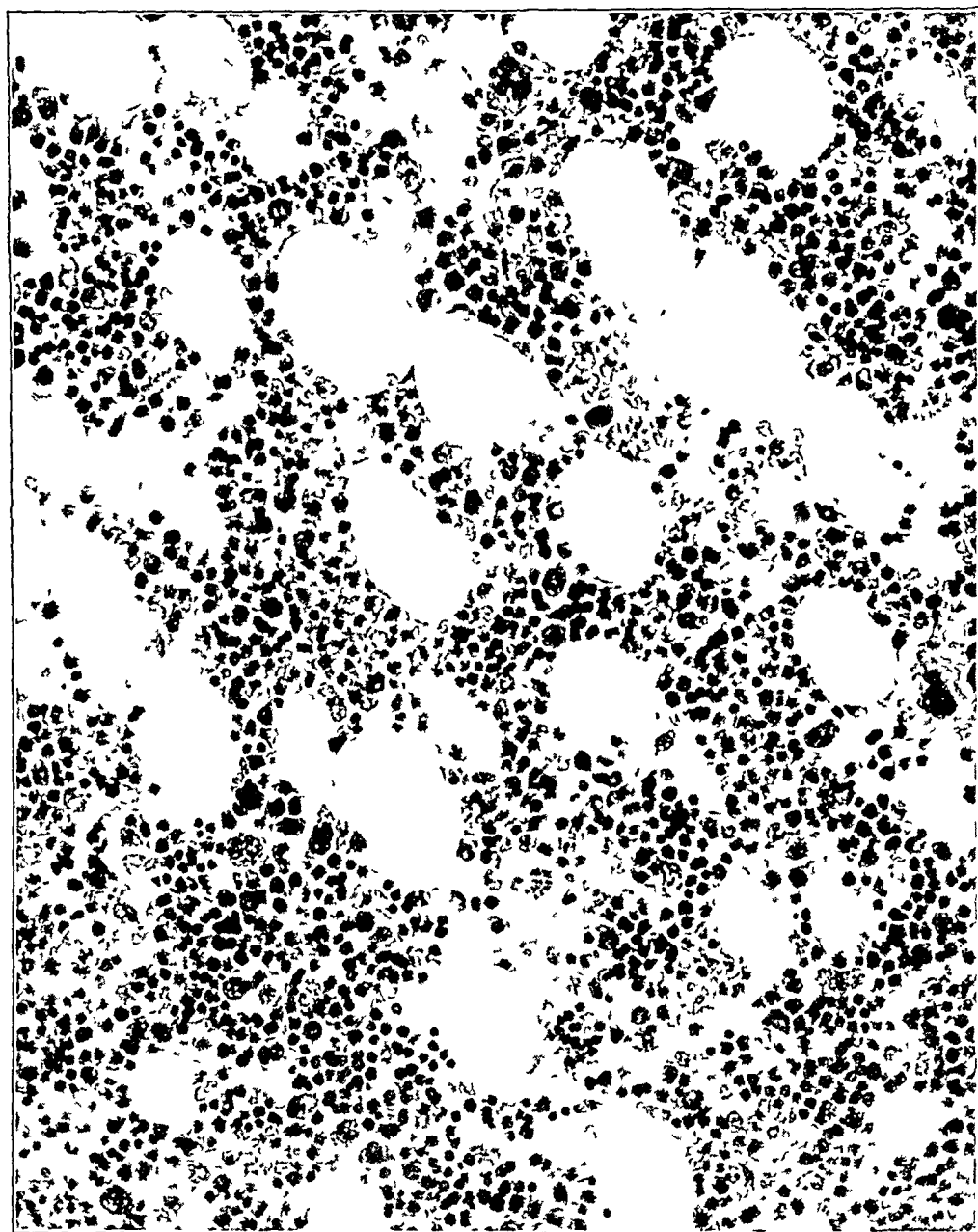


Fig 5 (dog 6) —Bone marrow ($\times 310$)

cedes the aplasia of the erythroblastic cells. Furthermore, these experiments emphasize the fact that individual variation in susceptibility to the toxic effects of the drug is difficult to evaluate in grams per kilogram. In these experiments, however, we were concerned only with the toxic effects of aminopyrine, and not with individual susceptibility. Such an experimental predication requires that the dose of the drug be graduated

to show its toxic effects rather than to find a susceptible animal to which the so-called therapeutic dose would be toxic

It is probable that if other drugs are fed in large quantities similar changes in the bone marrow would be produced. However, such a

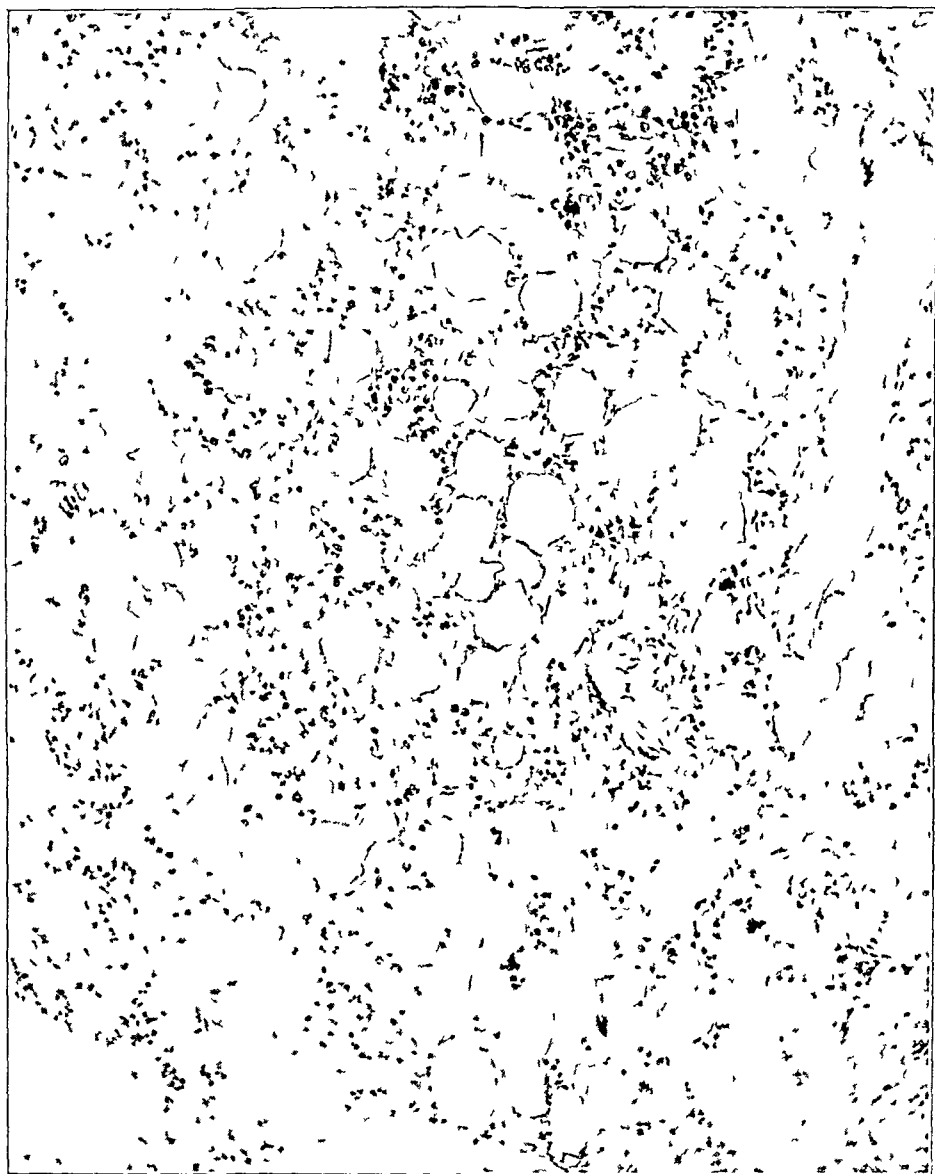


Fig 6 (dog 7) —Bone marrow ($\times 160$)

probability does not in any way detract from the fact that aminopyrine, aside from its direct systemic toxic action, has a selective action on bone marrow

The transference of these experimental results from dogs to man would be extremely hazardous and unscientific had we no more informa-

tion than is found in our experiments. However, there is considerable evidence to show that a small percentage of persons are extremely sensitive to aminopyrine and react by the development of neutropenia that may result in death. These and other facts found in our summary

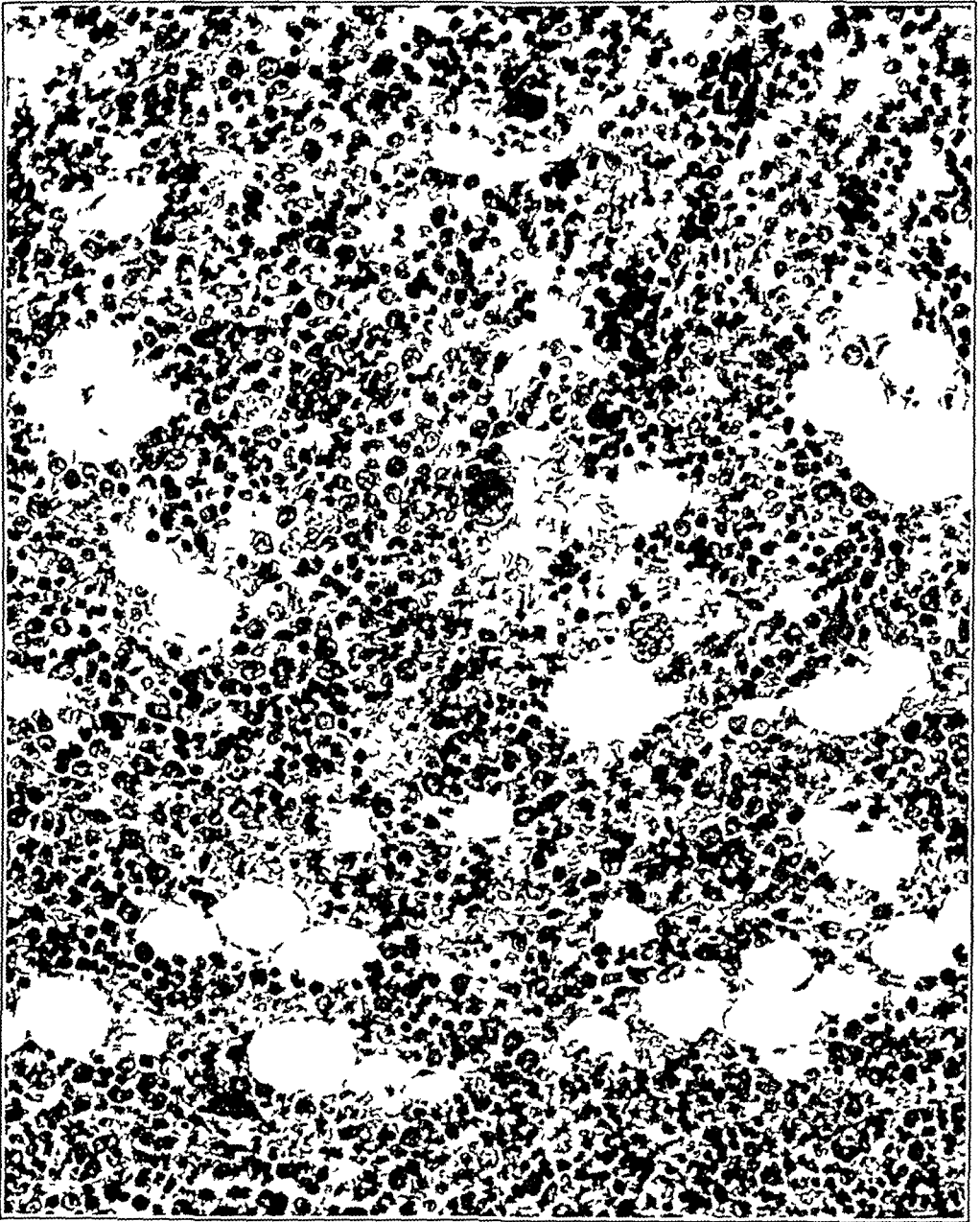


Fig 7 (control dog) —Bone marrow of the tibia ($\times 310$)

of the literature clearly establish aminopyrine as one of the causes of malignant neutropenia. Our experimental results merely establish the fact that aminopyrine has a selective toxic action on bone marrow.

It is our opinion that aminopyrine is only one of a variety of agents causing malignant neutropenia, although an important one.

CONCLUSIONS

It has been shown in these experiments that aminopyrine has a toxic effect on the bone marrow of dogs when administered orally in large doses

The end result is one of severe aplasia of the bone marrow, rather than of hyperplasia with "maturation arrest"

Neutropenia was noted in 1 of the 2 dogs having a markedly aplastic bone marrow

A summary of the literature on the experimental production of malignant neutropenia is presented

ANATOMIC OBSERVATIONS ON SEVENTY HOSPITAL PATIENTS AFTER SUDDEN DEATH

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AND

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Between Jan 1, 1927, and June 30, 1936, autopsies were performed on 70 patients who died suddenly in the wards of the New York City Hospital. All of these patients were sufficiently sick to require hospitalization, some being dangerously ill while others were ambulatory and comfortable. Death was sudden in the respect that it came on unexpectedly and occurred within twenty minutes of the initial symptoms. We have analyzed and grouped these cases, and we hereby report our observations.

The great majority of the deaths were cardiac. There were 49 patients, over two thirds of the total number, who gave anatomic evidence of fatal changes in the heart. The histologic data on many of these patients have been reported in detail by one of us¹. In 7 instances the cause of death was cerebral and in 4 pulmonary. Spontaneous rupture of the aorta accounted for 3 fatalities, ruptured aneurysm for 3, gastric accidents for 2, asphyxiation by a bolus of food for 1 and status lymphaticus for 1.

The cardiac causes could be arranged in eight subdivisions. Acute miliary infarction was the most prominent, being noted twelve times. Acute toxic myocarditis came next, with 10 instances. Acute coronary thrombosis followed, with 9 examples, and acute infectious myocarditis, with 7. The division of acute rheumatic infection consisted of 4 cases, acute interstitial involvement of 3, heart block of 2 and aortic stenosis of 1.

While we were able to arrange these cases in eight subdivisions, it was accomplished with no little difficulty. For example, 2 of the cases of acute miliary infarction could have been justifiably listed under infectious myocarditis. Bacterial emboli were noted in the myocardial branches of the coronary arteries in 1 case, and in another there was acute infectious endocarditis of coccic origin with thrombi in the coronary arterioles. Again, of the cases of interstitial

From the First Medical Division, service of Dr John Carroll, and the Pathological Laboratories, New York City Hospital, Department of Hospitals.

1 Lisa, J R. The Pathology of the Heart in Sudden Cardiac Death, *Ann Int Med*, to be published.

myocarditis, the condition in 1 was associated with acute lobar pneumonia, acute pericarditis and acute peritonitis. It would have been justifiable to include this with cases of infectious myocarditis. Furthermore, in 1 case listed under acute toxic myocarditis the disease was associated with acute lobar pneumonia, acute mediastinitis and acute pericarditis. The last 2 cases were not classed with those of infectious myocarditis, solely because organisms were not demonstrable within the myocardium.

The lesion we call acute miliary infarction has been reported by Roesler and Soloff². It consists of a small area of myocardial necrosis about the size of a low power microscopic field, sharply delimited and consisting practically of preexisting reticulum only, with remnants of myocardial cytoplasm, nuclei and lipochrome. Occasionally a few degenerating polymorphonuclear cells are seen at the periphery.

In all of our cases of coronary thrombosis the patients were in the old age group and showed extreme arteriosclerosis of the coronary arteries. In 6 cases only had there been associated clinical evidence of hypertension and arteriolosclerosis of the kidneys. Two patients were Negroes, a man and a woman, although coronary thrombosis is commonly believed to be a rarity in this race.

We observed 9 cases of acute toxic myocarditis and 8 cases of acute infectious myocarditis. In 5 cases of the infectious group the condition was associated with acute valvular endocarditis. In 3 of the cases there was syphilitic myocardial involvement, in 1 of which there was an acute rheumatic myocarditic lesion almost as extensive as the syphilitic lesion. In another case an unusual syphilitic manifestation consisted of arteritis affecting the myocardial branches of the coronary arteries, with softening proceeding to local thrombosis. In 6 of the 9 cases of toxic myocarditis there was associated acute pneumonia, in 1 of these cases streptococci were isolated, and in 1 there was a history of a recent infection of the upper respiratory tract.

The 4 cases of acute rheumatic myocarditis were characterized by an extraordinary number and wide distribution of Aschoff bodies. While sudden death in acute rheumatic heart disease is uncommon, it has been previously reported³.

The patients with heart block exhibited the Stokes-Adams syndrome. In 1 case the condition was complicated by a meningioma of the dura, while in the other only very mild fatty myocardial degeneration was apparent. Although the heart block was present in the latter case for over a year, the conduction system failed to show any histologic changes.

2 Roesler, H., and Soloff, L. A. *Ann Int Med* 9 477, 1935.

3 Rheumatic Heart Disease, Cabot Case 22041, *New England J Med* 214 154, 1936.

In the case of aortic stenosis there was extremely tight stenosis of the aortic valve with minimal lesions deep in the myocardium accompanied by lymphoid, plasma and a few polymorphonuclear cells

In 4 of the 7 cases of cerebral involvement the causes of death were proved at autopsy. They were, respectively, recent hemorrhage into the medulla, Torula meningoencephalitis, pontile hemorrhage and tumor of the brain. In the remaining 3 cases the general autopsy failed to reveal the cause of death, and the brains were not obtained, observation, however, suggested the probability of cerebral lesions

The pulmonary group consisted of 4 cases. In 3 of these death was due to pulmonary embolism. The origin of the embolism was not determined in 2 cases, but in the third it was observed to arise from extension into the vena cava of primary carcinoma of the kidney⁴. In the last case there was a massive hemorrhage from pulmonary tuberculosis

The ruptured aneurysms were all syphilitic. Two were thoracic and one was abdominal. Although this appears inconsistent with the known tendency for abdominal aneurysms to rupture, in the series of syphilitic aneurysms examined post mortem in the hospital, there was a much higher percentage of abdominal than of thoracic ruptures

In 2 of the 3 cases of acute rupture of the aorta the rupture had occurred in the intrapericardial portion of the aorta and resulted in hemopericardium. In both there was associated essential hypertension. In 1 there was the complication of syphilis, but this had affected the aorta well beyond the scene of rupture. In the third case the abdominal aorta was involved, and the point of rupture was near an arteriosclerotic plaque. It was of interest to note that in 1 case of thoracic rupture an infectious myocardial lesion was demonstrable histologically and that in the case of abdominal rupture extensive septicopyemia was present

In 1 case of gastric involvement death resulted from hemorrhage in a carcinoma, in another necropsy revealed perforation of a gastric ulcer with peritonitis

Asphyxia caused by a bolus of food in a patient with bulbar palsy accounted for 1 death, while another was due to status lymphaticus in a pregnant woman who was being anesthetized

RELATION OF POSTMORTEM TO CLINICAL DIAGNOSIS

We were interested to find in what percentage of cases the clinical diagnosis was correct. In 26, or about one third, of the cases the anatomic findings corroborated the clinical diagnosis. In 9 instances the clinical diagnosis was not correct, but could be considered reason-

⁴ Boyd, C. S., and Lisa, J. R. *J. Pediat.* 5:608, 1934

able In the remaining 35 cases the patients died of conditions not recognized by the clinicians

In the group of conditions that were correctly diagnosed, the outstanding involvement was acute coronary thrombosis, which occurred in 8 cases The clinical picture of this is distinctive, and as it is a commonly recognized cause of sudden death one would not be surprised to find a considerable degree of accuracy in the diagnosis In the cases of acute rheumatic myocarditis the disease was diagnosed clinically, while apoplexy, heart block and ruptured syphilitic aneurysm were each recognized as the cause twice In the remaining 9 cases the conditions varied in type and were easily recognized clinically

In 3 cases in which we designate the clinical diagnosis as reasonable a condition diagnosed as coronary sclerosis was seen to consist of acute miliary infarctions of the heart In 1 a condition diagnosed as spontaneous pneumothorax was a pulmonary embolism, in 1 a possible abscess of the lung was actually a tuberculous hemorrhage, and in 1, acute rheumatic fever, with presenting migrating arthritis for three weeks, proved to be acute endocarditis and myocarditis, probably meningococcic In 1 case a condition diagnosed as tuberculous meningitis was *Torula meningoencephalitis*, and in a case in which the diagnosis was toxic goiter with coronary sclerosis an inflammatory lesion of the myocardium was present A patient said to have pernicious anemia who died of a cardiac condition was considered at autopsy to have had acute toxic myocarditis

The clinical diagnosis in the remaining 35 cases did not explain the cause of death In 25 cases the anatomic diagnosis was myocarditis Of these, instances of miliary infarctions comprised the largest group, with toxic myocarditis second and infectious myocarditis third

The clinical features of acute miliary infarctions are those of acute left ventricular failure Miliary infarctions are usually diagnosed as coronary thrombosis because they occur most frequently in cases of recognized coronary sclerosis, and at autopsy they are practically always associated with the more severe grades of coronary sclerosis Acute toxic myocarditis is usually associated with pneumonia This is not generally appreciated by clinicians, although Gonzales found it occasionally during the pandemic of 1918-1919⁵ Infectious myocarditides are not diagnosed because other factors, such as syphilis and rheumatic heart disease, are more prominent and mask the features of the infectious element In our experience at the hospital infection superimposed on valves deformed by syphilis or rheumatism is much more frequent than the literature indicates On clinical grounds, this con-

5 Gonzales, T A Personal communication to the authors

dition can frequently be suspected because a sudden increase in cardiac symptoms occurs after a long period of slight variability

MAIN CAUSE OF DEATH A VASCULAR CONDITION

Our observations lead us to believe that the principal cause of sudden death may be considered as vascular. This is especially true when we employ "vascular" in the broad sense and include the heart as a modified blood vessel. Of the entire series, in 62 cases involvement was definitely of this character. In 5 cases only the condition was nonvascular, with 1 instance each of asphyxiation from a bolus of food, *Torula meningoenephalitis*, brain tumor, perforated gastric ulcer and status thymicolymphaticus. In the remaining 3 the cause probably was a cerebral vascular accident of embolic nature.

ROLE OF INFECTION

It was apparent that infection played a determining part in many of these cases of sudden death. In the majority of cases in the cardiac group there was evidence of an infectious or toxic factor affecting the myocardium. In 12 cases of the infectious group syphilis, rheumatism and the acute endocarditides accounted for death, in all with profound damage to the myocardium. The most prominent feature of the cases in the toxic group was the presence of acute pulmonary infections, which occurred in the great majority. This factor was particularly noticeable in infants and children. In the older patients the good condition of the coronary vessels was striking. Acute or chronic pulmonary infections were prominent also in the cases in which there was acute interstitial myocarditis. It was of interest to note that in 1 instance each in the infectious and in the toxic group acute pericarditis complicated the pneumonia. In a somewhat smaller percentage, but in more than half, of the cases of miliary infarcts, chronic pulmonary infections were present. In 1 instance bacterial masses were seen in the myocardial arterioles of the walls affected. In a second case acute arteriolar thrombi were present with acute endocarditis. We noted in the majority of the cases of this group the most severe grade of sclerotic changes of the coronary arteries. A toxic element was more difficult to prove in the cases of acute coronary thrombosis, but in 2 instances an acute glomerular lesion suggested that such a factor was present.

Spontaneous rupture of the aorta is generally believed to be due to acute medial necrosis of toxic origin, which occurs in an otherwise normal vessel. In 1 example in the present series, clinically mild pharyngitis had preceded by a few days the vascular accident. In this case an odd histologic finding in the heart was acute infectious myo-

carditis In 2 cases of miliary infarction, in both with minimal coronary arteriosclerosis, acute medial necrosis of the coronary vessels was associated with purulent bronchiectasis This lesion is similar to that which results in spontaneous rupture of the aorta

In the case of rupture of the arteriosclerotic aorta, a bacterial cause was not demonstrated The septicopyemia, however, strongly suggested that a local septic process had been present and had been destroyed by subsequent massive hemorrhage

SUMMARY AND CONCLUSIONS

Considering this report from a clinician's point of view, we note that about one third of the deaths were explainable by the clinical diagnosis There were also 9 cases in which the diagnosis was nearly enough correct to be considered reasonable One may say that the chances of making a correct diagnosis of sudden death under similar conditions are about 1/2 It is possible that the percentage of errors might be improved, as some of the patients whose condition was incorrectly diagnosed were not long enough in the hospital for a thorough study to be made

As one would expect, we found sudden death to be largely the result of a vascular accident In about 89 per cent of our cases the cause was proved to be of this nature Infection played a recognizable role in these fatalities Aside from syphilis, rheumatism and acute endocarditis, we observed that acute or chronic pulmonary infections were commonly associated This was particularly noticeable in children

We believe that one might arrive at a more perfect diagnostic score by giving greater consideration to the possibilities of the vascular, or perhaps the cardiovascular, aspect, especially when infection is present In 25 of the 35 cases in which the cause was unrecognized death was attributed to myocarditis In most if not all of these there was clinical evidence of concurrent infection Had the clinician been more conscious of the possibility of acute miliary infarction of the myocardium and acute toxic myocarditis in cases of this type, there would have been a larger percentage of correct diagnoses It would be reasonable to say that in 55 or more of the 70 cases the condition could have been correctly diagnosed if these pathologic changes were more commonly known to clinicians

ROENTGENOGRAMS OF THE CHEST AND THE INTRACUTANEOUS TUBERCULIN TEST FOR ADULTS

A COMPARATIVE STUDY

LUKE W HUNT, M D

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For many years investigators have striven to evolve some sort of test which would help in the diagnosis of tuberculosis. In 1907 von Pirquet brought forth his well known cutaneous test, and soon several modifications of the test were introduced, including the Mantoux intracutaneous test, which has so well stood the test of time that at present it is used more extensively than any of the others. The value of the Mantoux test as an aid in establishing a diagnosis of tuberculosis in infancy and early childhood has been accepted for many years. Reports of its value in adult life have been received with varying degrees of approbation and distrust, and only in recent years has it been found to have a definite place, when properly performed and interpreted, as an aid in establishing a diagnosis of tuberculosis in older patients.

The lack of agreement as to the value of the intracutaneous tuberculin test for adults may be due to the facts that it is generally used as a qualitative test and that in routine testing dilutions of 1:100, 1:1,000 and 1:10,000 are used. There is, moreover, no general agreement as to what constitutes a positive reaction. Atsatt¹ in reporting a series of tuberculin tests on 211 patients with tuberculosis of bones and joints stated that the reactions were read in 6 degrees of intensity but did not describe the reaction which he interpreted as positive. He used dilutions of 1:1,000, 1:2,500, 1:5,000 and 1:10,000, the 1:10,000 dilution was considered as diagnostic. King,² in another series of tests, using a 1:20,000 dilution as diagnostic, considered a positive reaction to be an area of erythema, nearly always indurated, 1 cm or more in diameter. Blair and Galland³ stated that their criterion for a positive reaction

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1 Atsatt, R. F. Studies with a Quantitative Tuberculin Reaction, *J. Bone & Joint Surg.* **9** 657 (Oct.) 1927

2 King, R. B. A Tuberculin Test of Value in Adults, *New England J. Med.* **207** 831 (Nov. 10) 1932

3 Blair, J. E., and Galland, W. L. A Differential Quantitative Tuberculin Test, *Am. Rev. Tuberc.* **23** 1 (Jan.) 1931

is the formation of an indurated cutaneous nodule, whatever its size, usually accompanied by erythema. They used dilutions of 1 10,000, 1 100,000, 1 1,000,000 and 1 10,000,000. The 1 100,000 dilution was considered diagnostic. Ayman,⁴ using dilutions of 1 10,000 to 1 10,000,000, with the 1 50,000 dilution as diagnostic, considered a positive reaction to be an area of erythema 10 by 9 mm or more, nearly always indurated. Moncrieff,⁵ reporting a series of qualitative tuberculin tests of children with dilutions of 1 100, 1 1,000 and 1 10,000, stated that a positive reaction consists of a red area of swelling, easily palpable, frequently tender and with an average diameter of 2 cm. He also stated that erythema alone without a palpable swelling is not sufficient for a reaction to be called faintly positive. Opie and McPhedran⁶ in their investigation assumed that an area of redness 10 mm or more in diameter indicates a positive reaction and stated that "inconspicuous spots of redness or redness with no edema have not been regarded as definite evidence of hypersensitiveness to tuberculin." Hart,⁷ on the other hand, stated that "a reaction should be regarded as positive if it consists of an area of erythema or erythematous infiltration the greatest diameter of which equals or exceeds 5 mm." Cummins and Walker⁸ even considered that "no reaction measuring less than 2 mm across can be accepted as definite."

Not only is there no general agreement as to what constitutes a positive tuberculin reaction, but some of the technics reported in the literature are open to question. In some instances the tests have been performed by different persons and the results interpreted by nurses and interns, unless such workers have had a good deal of experience with the tests the percentage of error is likely to be high. Cummins and Walker stated that their object was to raise a wheal about the size of a threepenny piece, and they paid more attention to the attainment of this effect than to the absolute amount of fluid injected, although the average volume was "round about 0.1 cc."

It is generally agreed that the qualitative tuberculin test with the dilutions commonly used is of value in establishing a diagnosis of

4 Ayman, D. The Intracutaneous Quantitative Tuberculin Test in the Diagnosis of Active Tuberculosis, *J A M A* **103** 154 (July 21) 1934.

5 Moncrieff, A. The Clinical Interpretation of the Intradermal Tuberculin Reaction, *Quart J Med* **24** 153 (Jan) 1931.

6 Opie, E. L., and McPhedran, F. M. The Contagion of Tuberculosis, *Am Rev Tuberc* **14** 347 (Oct) 1926.

7 Hart, P. D. A. The Value of Tuberculin Tests in Man, Medical Research Council, Special Report Series, no 164, London, His Majesty's Stationery Office, 1932, p 126.

8 Cummins, S. L., and Walker, S. B. H. Investigation and Assessment of One Hundred Cases of Pulmonary Tuberculosis, *Tubercle* **12** 436 (July) 1931.

tuberculosis only for infants and very young children and is of extremely limited value for adults. The quantitative factor, or the measure of the degree of hypersensitivity to tuberculin, has been greatly neglected. From the time of the earliest description of the tuberculin reaction there has been a semblance of the belief that there is a relation between the degree of sensitivity to tuberculin, as shown by the cutaneous reaction, and the extent of the tuberculosis in the person being tested. Thus von Pirquet required for a positive reaction an area of erythema not less than 5 mm in diameter. Mantoux's technic demanded the intradermal injection of 1 drop of a 1:5,000 dilution of tuberculin. Both investigators thus presupposed a quantitative element in these tests. It appears plausible that active tuberculous disease, with continual reaction of the patient to repeated liberation of toxic material from the focus of activity, is accompanied by a degree of hypersensitivity different from that associated with a latent infection or a long-continued process of healing, in which the escape of toxic substance from a focus is inhibited or prevented by walling off. By administration of a series of graded dilutions of tuberculin it should be possible to establish a point above which reactions can be obtained only in those who possess a considerable degree of hypersensitivity, that is, persons actively combating tuberculous disease.

This paper describes an effort to correlate the local reactions to the intracutaneous injections of different dilutions of commercial old tuberculin with the roentgen findings in the chests of 460 healthy young adults and 45 young adults with active lesions, the object being to evaluate the cutaneous reactions in terms of past or present tuberculous infection in the lungs. It also includes a brief discussion of some of the problems encountered in such a study.

MATERIAL

Two groups of young adults were used for the study. The first group consisted of 232 nurses ranging in age from 18 to 30 years. They were in good health at the time of the tests and had passed physical examinations when they began training. They were considered a homogeneous group, perhaps representing better health than a group of the same age chosen at random. The second group consisted of 230 healthy graduate nurses, interns and attendants and 43 adults who were found to have active lesions on routine physical examination. Their ages varied from 20 to 35 years, approximately 95 per cent were between 20 and 30.

METHOD

The tuberculin tests were performed by the intradermal injection of 0.1 cc of different dilutions of commercial old tuberculin into the flexor surfaces of the forearms and one injection of 0.1 cc of the diluting fluid for control. The diluting fluid contained 0.2 per cent phenol in an 0.85 per cent solution of sodium chloride. For the first group 1:1,000 and 1:5,000 dilutions were used and for the second

group 1 10,000 and 1 100,000 The dilutions were made fresh each week MacGregor syringes containing 1 cc and graduated in tenths and 27 gage needles were used All reactions to tests and controls were measured for induration and redness after twenty-four and forty-eight hours and the majority also after seventy-two hours All the tests and readings for the two groups were done by the same person

The reactions were divided according to severity into the following groups

Group	Reaction (Induration), Mm
0	None
1	10 by 10 to 15 by 15
2	15 by 15 to 20 by 20
3	20 by 20 to 30 by 30
4	30 by 30 and above

The roentgen plates of the chests were studied with regard to signs of past and present infection Naturally in this group many of the plates were considered normal from the roentgenologic standpoint, but the following divisions were made

Group	Reading
I	Completely negative
II	Large irregular calcifications in hilus, parenchyma or both
III	Signs of present activity

The results are recorded in the table It will be seen that in group I, those whose roentgenograms were completely negative, 131, or 62.4 per cent, gave a negative reaction to the 1 1,000 dilution and 79, or 37.6 per cent, a positive reaction, with the 1 5,000 dilution, 169, or 80.4 per cent, gave a negative and 41, or 19.6 per cent, a positive reaction, with the 1 10,000 dilution, 176, or 83.8 per cent, gave a negative and 34, or 16.2 per cent, a positive reaction, with the 1 100,000 dilution, 203, or 96.7 per cent, reacted negatively and 7, or 3.3 per cent, positively In group II, those with large irregular calcifications in the hilus or parenchyma, 9, or 4.5 per cent, gave a negative reaction and 11, or 5.5 per cent, a positive reaction to the 1 1,000 dilution With the 1 5,000 dilution, 12, or 6.0 per cent, had a negative and 8, or 4.0 per cent, a positive reaction, with the 1 10,000 dilution, 15, or 7.15 per cent, had a negative and 5, or 2.85 per cent, a positive reaction and with the 1 100,000 dilution, 20 had a negative and none a positive reaction

In group III, those with roentgen evidence of present activity, only 2 were tested with the 1 1,000 and the 1 5,000 dilution, and both had positive reactions With the 1 10,000 dilution and the 1 100,000 dilution, 41, or 94.8 per cent, gave a positive and 2, or 4.6 per cent, a negative reaction Hence with 1 1,000 and 1 5,000 dilutions of old tuberculin there seems to be no correlation between the cutaneous reactions and the roentgen findings of the chests of young adults sufficient to

*Comparison of Roentgenograms of the Chest and Intracutaneous Tuberculin Reactions of Five Hundred and Five Young Adults
with 1 1,000, 1 5,000, 1 10,000 and 1 100,000 Dilutions of Old Tuberculin*

		1 1,000 Dilution							1 5,000 Dilution						
		Reaction (Induration), Mm							Reaction (Induration), Mm						
Group	Roentgen Findings	Number of Negative Results	10 by 10 to 15 by 15	15 by 15 to 20 by 20	20 by 20 to 30 by 30	30 by 30 or Above	Total	Number of Negative Results	10 by 10 to 15 by 15	15 by 15 to 20 by 20	20 by 20 to 30 by 30	30 by 30 or Above	Total		
I	Completely negative	131 (62 1%)	16	13	13	43 (37 6% positive)	210	169 (80 4%)	19	13	9	0 (19 6% positive)	210		
II	Large irregular calcifica tions in hilus, parenchyma or both	9 (45%)	0	1	2	8 (55% positive)	20 — 230	12 (60%)	5	3	0	0 (10% positive)	20 — 230		
III	Signs of present activity			1	1		2		0	1	1	0	2		
		1 10,000 Dilution							1 100,000 Dilution						
I	Completely negative	176 (83 8%)	23	11	0	0 (16 2% positive)	210	203 (96 7%)	3	4	0	0 (3 3% positive)	210		
II	Large irregular calcifica tions in hilus, parenchyma or both	15 (71 5%)	4	1	0	0 (28 5% positive)	20 — 230	20 (100%)	0	0	0	0	20 — 230		
III	Signs of present activity	2 (5 2%)	0	11	14	16 (91 8% positive)	13	2 (5 2%)	7	13	12	9 (94 8% positive)	13		

be of worth in evaluating the past or present activity of tuberculous infection in the lungs. But response to a dilution of 1:100,000 may usually be considered indicative of active tuberculosis, and response to the 1:10,000 and not to the 1:100,000 dilution seems to indicate latent or healed tuberculosis.

It should be stated that of the 7 subjects who had negative roentgenograms and who had a positive reaction to the 1:100,000 dilution, 3 had a history of contact. One, a nurse, had just finished a course of training at a tuberculosis sanatorium, another, an intern, had finished an internship at a similar institution, and the third was a man whose wife had tuberculosis. One of the others had rather extensive calcifications in the hilus and parenchyma. The significance of definite evidence of calcification in the hilar region or in the parenchyma has only recently been appreciated. Pathologists have shown that unless these lesions are completely calcified they should not be looked on as healed. For a discussion of this subject the reports of Hektoen,⁹ Opie and Aronson¹⁰ and, more recently published, Feldman and Baggenstoss¹¹ should be consulted. At any rate, the roentgenogram gives little information on what is happening within and immediately around these deposits. This is well illustrated by 1 of the group, who had a positive reaction to the 1:100,000 dilution and whose roentgenograms showed extensive calcification in the hilus and parenchyma. The roentgenograms were considered to show normal conditions except for the calcifications. About a year after the first plates were taken an exploratory laparotomy was done, and the patient was found to have tuberculous peritonitis. Roentgenograms made on several occasions before the operation showed no change from the original plates, but the primary focus was probably in the lungs.

The 2 adults who had roentgen evidence of active lesions and whose tuberculin reactions were negative had small areas of infiltration about 3 mm in diameter in the subapical region but no other evidence of tuberculosis. Unfortunately, further testing of these subjects could not be done.

It should be stated also that the majority of the patients with active lesions had a minimal exudative type of tuberculosis. Westwater¹²

9 Hektoen, L. Tubercle and Morbid Anatomy, in Klebs, A. C. Tuberculosis. A Treatise by American Authors, New York, D. Appleton and Company, 1909, chap. 2, pp. 52-79.

10 Opie, E. L., and Aronson, J. D. Tubercle Bacilli in Latent Tuberculous Lesions and in Lung Tissue Without Tuberculous Lesions, *Arch. Path.* **4**:1 (July) 1927.

11 Feldman, W. H., and Baggenstoss, A. H. The Residual Infectivity of the Primary Complex of Tuberculosis, *Am. J. Path.* **14**:473 (July) 1938.

12 Westwater, J. S. Allergy in Tuberculosis. The Quantitative Use of the Mantoux Test, *Tubercle* **15**:543 (Sept.) 1934.

concluded from his work that the young adult with exudative disease tends to have higher sensitivity than the older subject with the fibroid type, i e, the more recent and active the disease, provided it is not massive, the higher the sensitivity

In the group with active lesions the cutaneous reactions were usually larger than in the other groups. None of the positive reactions in the group with active lesions measured less than 10 by 10 mm. However, the size of the reaction is perhaps not as important as the degree. It is obvious that an area of 20 mm in diameter showing simple infiltration means less sensitivity than a reaction of the same size showing necrosis. In our experience induration is the most important criterion of a positive reaction. Erythema alone is unreliable. It is occasionally seen in sensitive skins, in case of Negro patients it is often impossible to judge the presence of erythema. In this series, at least, the most intense reactions showed induration, pale yellow edema and occasionally vesiculation.

These results indicate that the quantitative tuberculin test is a valuable confirmatory diagnostic procedure in early adult life and is perhaps as valuable an aid as the qualitative test in infancy and early childhood. In case of infants and young children one is usually dealing with the first infection type of tuberculosis, while in case of adults it is the reinfection type. To use the words of von Pirquet, the first group as a rule has not "met the tubercle bacillus," while the second group has done so. It is well known that certain conditions modify the tuberculin reaction, but these conditions are usually obvious and have to be taken into consideration when one interprets the test. It is also well known that a tuberculin test and a roentgen examination of the chest do not constitute complete examination for tuberculosis. They only provide evidence that may be used by the clinician in conjunction with the history and with results of physical and laboratory examination in arriving at a final diagnosis. However, probably the best method of selecting subjects for such an examination is the use of the quantitative tuberculin test and roentgenograms.

CONCLUSIONS

Intracutaneous tuberculin tests were performed on a group of 505 young adults with different dilutions of old tuberculin, and the results were compared with roentgen evidence of past or present tuberculous infection in the lungs.

With 1 1,000, 1 5,000 and 1 10,000 dilutions of old tuberculin there was not sufficient correlation between the cutaneous reactions and the roentgen findings to be of worth in evaluating the past or present activity of tuberculous infection in the lungs.

With the 1:100,000 dilution, however, 96.7 per cent of 230 young adults whose roentgenograms were negative gave a negative reaction and 3.3 per cent a positive reaction. With the same dilution, 41, or 94.8 per cent, of 43 young adults who had roentgen and other evidence of active tuberculosis gave a positive reaction and 2, or 5.2 per cent, gave a negative reaction.

None of the positive reactions in those with active lesions had an area of induration measuring less than 10 by 10 mm. Induration is considered the most important criterion of a positive reaction. Erythema alone is unreliable.

The quantitative intracutaneous tuberculin test is a valuable aid when used in conjunction with other available data in establishing a diagnosis of tuberculosis in young adults. Its accuracy when it is properly performed and interpreted is comparable to that of the commonly accepted immunologic and serologic diagnostic procedures.

TEST OF GLOMERULAR FUNCTION WITH SODIUM FERROCYANIDE

FURTHER STUDIES

EDWARD J STIEGLITZ, M D

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The first clinical studies on the urinary excretion of sodium ferrocyanide as a criterion of glomerular efficiency were reported in 1934¹ It was then shown that the curves for the excretion of this salt by normal persons are characteristic and have but little variation In the succeeding four years additional data have been obtained, and these continued studies have further clarified the application of the test

METHOD

There has been no significant change in the technic previously reported Ampules of sterile dry pure sodium ferrocyanide containing 0.5 Gm of the hydrated salt, or about 0.25 Gm of the anhydrous salt, were employed Ferrocyanide salts might be decomposed by the gastric acid if taken orally, but on slow intravenous injection no evidences of toxic effects have been observed

The contents of one ampule are dissolved in 10 cc of sterile distilled water and administered by slow intravenous injection It is essential that this solution be clear before the injection is started, the salt dissolves rather slowly Specimens of urine are collected thirty, sixty, one hundred and twenty and one hundred and eighty minutes after the injection and their content of ferrocyanide determined by analysis It is immaterial just how much water is consumed before or during the test, the rate of excretion appears to be independent of the volume of urine Ample fluid to make possible the prompt voiding of urine at the proper intervals is desirable

The titration of ferrocyanide is carried out with a 0.4 per cent solution of cupric sulfate (0.004 Gm per cubic centimeter) Before titration the specimen is acidified with concentrated sulfuric acid Cupric ferrocyanide is a slightly soluble red salt but is more soluble than the well known prussian blue (ferriferrocyanide) To determine the end point in titration, drops of solution of ferric chloride are placed on a tile, and as the titration proceeds a drop of the unknown is placed in contact with the ferric chloride If free ferrocyanide is present prussian blue is imme-

From the Department of Medicine of the Chicago Memorial Hospital

Ampules of sterile dry pure sodium ferrocyanide were supplied by the Abbott Laboratories

1 Stieglitz, E J, and Knight, A A Sodium Ferrocyanide as Clinical Test of Glomerular Efficiency Preliminary Report, J A M A **103** 1760 (Dec 8) 1934

diately formed, if all the ferrocyanide has already been precipitated as cupric ferrocyanide, a distinct delay occurs before the appearance of this blue color. The end point is therefore read when the appearance of the blue is delayed four to five seconds.

The calculation is based on the chemical equation $\text{Na}_4\text{Fe}(\text{CN})_6 + 2 \text{CuSO}_4 \rightarrow \text{Cu}_2\text{Fe}(\text{CN})_6 \downarrow + 2 \text{Na}_2\text{SO}_4$. The molecular weight of $\text{Na}_4\text{Fe}(\text{CN})_6$ is 304.08 and that of $\text{CuSO}_4 \times 2$ is 319.26. If the solution of cupric sulfate contains *exactly* 0.004 Gm per cubic centimeter, then 1 cc of the solution precipitates exactly 0.0038 Gm, or 1.52 per cent, of the injected dose of 0.25 Gm of anhydrous sodium ferrocyanide. The exact strength of the cupric sulfate is best first measured by electrolytic methods.

REVIEW OF PREVIOUS WORK

The application of sodium ferrocyanide to clinical study of the glomerular efficiency of the kidneys is based on the premise that ferrocyanide salts are excreted solely by the glomeruli. This almost unique distinction was first noted by Marshall and Grafflin² when they observed that the practically aglomerular kidneys of *Lophius piscatorius* eliminated no ferrocyanide or only 0.2 to 0.5 per cent of the quantity eliminated by fish with glomerular kidneys.³ Histochemical studies on mammalian kidneys by Gersh and Stieglitz,⁴ who utilized the highly accurate Altmann freezing-drying technic,⁵ or rapid perfusion with a solution of cupric sulfate to fix the ferrocyanide, revealed that in the normal rabbit ferrocyanide is eliminated entirely via the glomeruli. No evidence of tubular excretion was discovered. Identical distribution of ferrocyanide in the tissues of the kidneys of dogs and monkeys has since been observed by Gersh.⁶ The excretion of ferrocyanide ceases when arterial tension is reduced by section of the medullary portion of the spinal cord. This behavior is in sharp contrast to that of ferric salts, which are excreted by the proximal convoluted tubules and whose excretion continues despite acute hypotension,⁷ but at a rate which corresponds to the characteristically great drop in excretion of creatinine which was observed on lowering the arterial tension in normal men by spinal anesthesia.⁸

Extensive studies by Van Slyke, Hiller and Miller⁹ on the ferrocyanide clearance in dogs showed that ferrocyanide, inulin and creat-

2 Marshall, E. K., Jr., and Grafflin, A. L. *Bull. Johns Hopkins Hosp.* **43**: 205 (Oct.) 1928.

3 Marshall, E. K., Jr. *Am. J. Physiol.* **94**: 1 (July) 1930.

4 Gersh, I., and Stieglitz, E. J. *Anat. Rec.* **58**: 349 (March 25) 1934.

5 Gersh, I. *Anat. Rec.* **53**: 309 (Aug. 25) 1932.

6 Gersh, cited by Van Slyke, Hiller and Miller,^{9a} p. 613.

7 Stieglitz, E. J. *Am. J. Anat.* **29**: 33 (May) 1921. Holton, S. G., and Bensley, R. R. *ibid.* **47**: 241 (March) 1931.

8 Lassen, H. C. A., and Husfeldt, E. *J. Clin. Investigation* **13**: 263 (March) 1934.

9 Van Slyke, D. D., Hiller, A., and Miller, B. F. (a) *Am. J. Physiol.* **113**: 611 and (b) 629 (Nov.) 1935.

mine follow the same excretory behavior, as their plasma clearances are equal and independent of the concentrations of plasma. They concluded that the plasma clearance of ferrocyanide, like that of inulin and/or creatinine, is equal to the glomerular filtration in dogs. Ferrocyanide and inulin were found not to enter the erythroplasts to any appreciable degree but to remain in the blood plasma, whereas urea diffuses rapidly to maintain intracellular equilibrium with the concentration of plasma.^{9b} The urea clearance in dogs is about half the clearance of ferrocyanide, inulin or creatinine. It is assumed that urea is reabsorbed by the tubules whereas the other substances are not. Actually there is no convincing proof of the reabsorption of the solute by the tubules. That water (the solvent) is reabsorbed in the distal convoluted tubules is unquestioned. The assumption of the reabsorption of the solute by these tubules becomes necessary only when one utterly denies the existence of possible excretory activity on the part of the proximal convoluted tubules. Such denial is unwarranted.

Miller and Winkler¹⁰ studied the sodium ferrocyanide clearance in man, using the analytic methods of Edwards and Langley.¹¹ Their results indicated close parallelism between the ferrocyanide clearances and the urea clearances, whereas the inulin clearances were nearly twice as great. These results are markedly different from those obtained with dogs,^{9a} in which essentially identical excretory behavior was noted with creatinine, inulin and ferrocyanide. Miller and Winkler concluded that the mechanisms for excreting ferrocyanide in man and in the dog are not the same, that in man the salt may be reabsorbed (as urea is presumed to be) and that therefore the excretion of ferrocyanide in man does not necessarily parallel glomerular filtration. This apparent discrepancy requires confirmation of the data by different methods. It does not invalidate the clinical application of the excretion of ferrocyanide to the study of glomerular efficiency, for there is no evidence whatever indicating that ferrocyanide is excreted via any other route than through the glomeruli. In these studies with patients Miller and Winkler¹⁰ employed doses of sodium ferrocyanide from three to twenty-four times larger than those originally used and recommended by Stieglitz and Knight.¹ These huge doses caused renal irritation.

Clinical comparison by Gordon¹² of the results of the test for excretion of sodium ferrocyanide with the results of a simultaneous urea clearance test revealed a coefficient of correlation of 0.7. It was observed also that the excretion of ferrocyanide did not alter the urea clearance. Gordon concluded that for practical clinical purposes the two tests gave

10 Miller, B. F., and Winkler, A. *J. Clin. Investigation* **15** 489 (Sept.) 1936.

11 Edwards, J. G., and Langley, W. D. *J. Biol. Chem.* **112** 469 (Jan.) 1936.

12 Gordon, W. *Am. J. M. Sc.* **192** 208 (Aug.) 1936.

fundamentally parallel results Baker and Habein,¹³ employing the technic of Stieglitz and Knight, studied the excretion of ferrocyanide in cases of urinary obstruction. The reduction in excretion of ferrocyanide in their cases of prostatic obstruction paralleled the reduction of phenolsulfonphthalein output. Despite the severe renal impairment of many of their patients, no systemic toxic symptoms were noted in any case. It is remarkable, however, that when prostatic irritation exists, injection of ferrocyanide causes marked urethral and prostatic burning for one to two hours, the intensity of this local pain varies with the frequency of previous catheterization. The greater the urethral irritation and inflammation prior to the administration of ferrocyanide, the greater the discomfort. I also have observed this form of local reaction in elderly men and have refrained from employing sodium ferrocyanide for patients with known urethral irritation.

RESULTS

The previously reported series of tests made on persons with apparently normal renal function has now been extended to include tests on 150 such persons. The second series of tests yielded means slightly higher than those reported in 1934. The comparison of the results is shown in table 1.

A revised curve of the normal rate of excretion (chart 1) shows but minor shift from the rate previously considered normal. For the sake of convenience and clinical simplicity, it is adequate to consider the average normal output to be in the neighborhood of 15 per cent of the injected dose for the first thirty minutes, 25 per cent at the end of an hour and 35 and 45 per cent respectively after two and three hours.

Calculations based on the percentage of the injected dose excreted do not take into consideration the fact that the ferrocyanide available in the blood is constantly diminishing. There is no way of determining the rate of excretion in reference to the concentration of the blood except by "clearance" studies including determination of the ferrocyanide content of the blood.⁹ In man this is not feasible, as the present methods for quantitation of ferrocyanide are too insensitive to permit measurement of minute quantities and therefore inadvisably large doses of the salt would be required. However, it is possible, with the present data, to correct the percentages of ferrocyanide excreted, allowing for that eliminated in the previous interval. It is true that this does not take into consideration the salt which may diffuse into tissues other than the kidneys. However, such diffusion as does occur probably takes place almost immediately after the injection of the salt and is therefore

¹³ Baker, G. S., and Habein, H. C. Proc. Staff Meet., Mayo Clin. **11** 134 (Feb. 26) 1936.

a relatively constant source of error. When the calculations are revised the data unquestionably more closely approximate the true excretory rate than when the previously excreted ferrocyanide is ignored.

For example, in the normal person, 15.4 per cent of the injected ferrocyanide is eliminated in the first thirty minutes after injection and an additional 12.3 per cent in the second half hour. However, in this second interval only 84.6 per cent of the dose originally injected is theoretically available for excretion, and therefore the rate of excretion is actually higher than 12.3 per cent. For convenience and clarity, one may speak of the revised calculations as "corrected percentages."

TABLE 1—*Ferrocyanide Output of Normal Patients* *

Time (Min.)	50 Patients (1934)	150 Patients (1938)
30	13.5	15.4
60	8.5 22.0	12.3 27.7
120	9.0 31.0	9.8 37.5
180	10.0 41.0	6.5 44.0

* Recorded in percentage of the injected dose excreted.

TABLE 2—*Comparison of "Uncorrected" and "Corrected" Rates of Excretion of Normal Persons*

Time (Min.)	"Uncorrected" Normal Rate of Excretion (Percentage of the Injected Dose)	"Corrected" Normal Rate of Excretion (Percentage of the Salt Remaining in the Body)
30	15.4	15.4
60	12.3	14.54
120	9.8	13.55
180	6.5	10.41

Recalculation along such lines reveals some most suggestive data. A comparison of the uncorrected and the corrected percentages of excretion is shown in table 2.

As is to be expected, the decline in percentage of excretion of the theoretically available sodium ferrocyanide is much smaller. This relation is better visualized when these data are diagrammed, as in chart 2. As previously stated, the "correction" does not take into consideration the diminution in the supply of ferrocyanide due to diffusion into tissues other than the kidneys, but this is probably not as serious a source of error as one first suspects. Ferrocyanide salts are extremely diffusible, and such disappearance from the blood stream into tissues probably takes place with great rapidity almost immediately after the intravenous injection of the salt. It is highly probable that after the first few minutes there exists a fairly stable equilibrium between the content of

ferrocyanide in the blood and that in the tissues By far the greatest quantity of ferrocyanide is eliminated in the first hour

Application of the test of glomerular function to the study of renal impairment in hypertensive arterial disease confirmed the findings

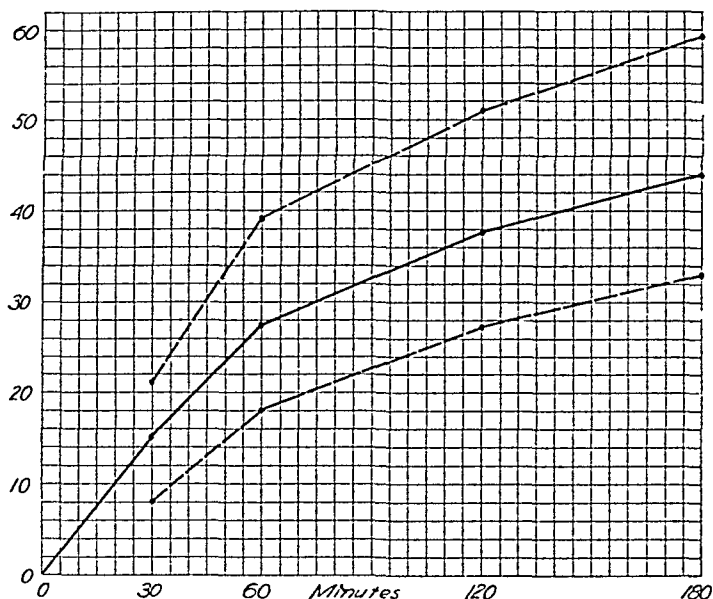


Chart 1—Mean excretion of sodium ferrocyanide of 150 patients with presumably normal kidneys The spread of variation is shown by dash lines The values are recorded in terms of the percentage of the injected dose eliminated

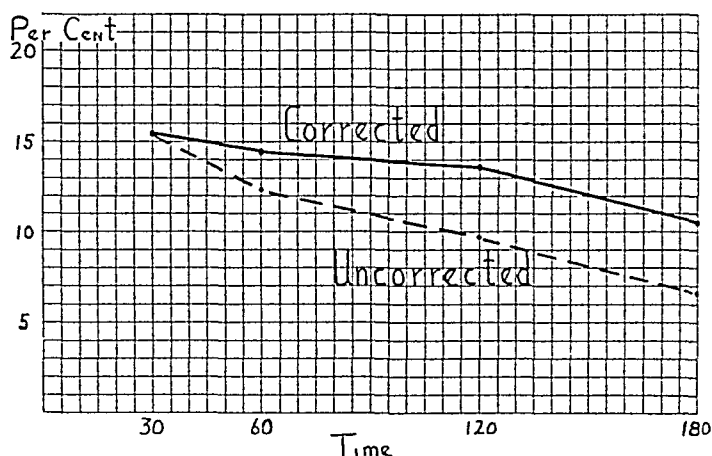


Chart 2—Mean normal rates of excretion of ferrocyanide calculated in terms of percentage of the total injected dose (broken line) and "corrected" on the basis of the amount of ferrocyanide remaining within the body (solid line)

recorded in the preliminary report¹ For some 80 additional cases of hypertensive disease the mean rate of excretion and the observed extremes are shown in chart 3 in terms of the percentage of the injected

dose of salt eliminated at the four routine intervals, thirty, sixty, one hundred and twenty and one hundred and eighty minutes after the injection. As previously observed, the most conspicuous impairment exists in the first hour of the test. In the 80 cases of hypertensive

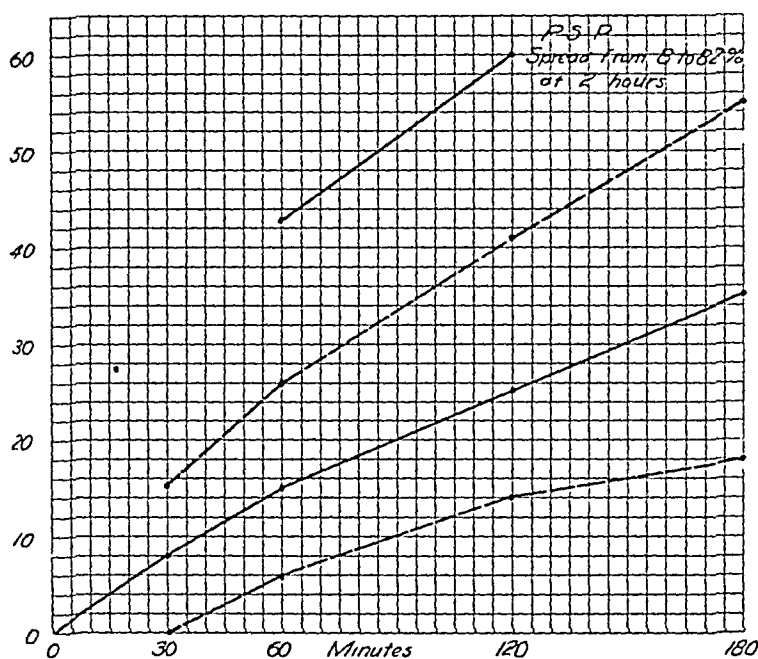


Chart 3—Excretion of ferrocyanide in 80 cases of hypertensive disease of the arteries. The solid line represents the mean, the dash line, the extremes observed. The values are based on percentages of the injected dose.

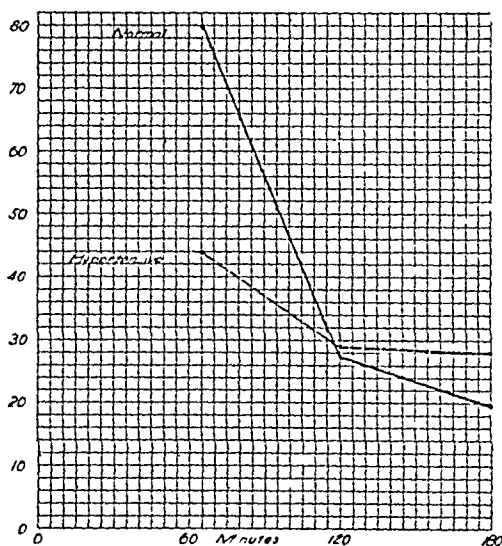


Chart 4—Milligrams of ferrocyanide excreted by normal and by hypertensive patients (means).

arterial disease the average delay in excretion in the first hour is clearly seen in the curve when chart 3 is compared with the normal curve in chart 1. In the third hour the rate of excretion is much the same in hypertensive as in normal patients, if recorded in milligrams of

sodium ferrocyanide excreted (chart 4), the excretion of hypertensive patients in the last hour is actually greater than that of normal patients.

Analysis of the average excretion of sodium ferrocyanide of the 80 hypertensive patients by "correcting" the percentage of elimination for the amount of ferrocyanide already excreted reveals most interesting data (chart 5). Whereas for patients with the normal type of response the percentage of salt eliminated is at first high and then gradually declines, for hypertensive patients the curve of the mean percentage eliminated is a *rising* line. This rate is almost uniform throughout the three hour test. The spread of difference between it and the normal rate gradually diminishes, until in the third hour the rates are almost identical, the mean normal excretion being 10.41 per cent of the ferrocyanide remaining within the body and the mean excretion of patients with hypertensive arterial disease being 10.2 per cent.

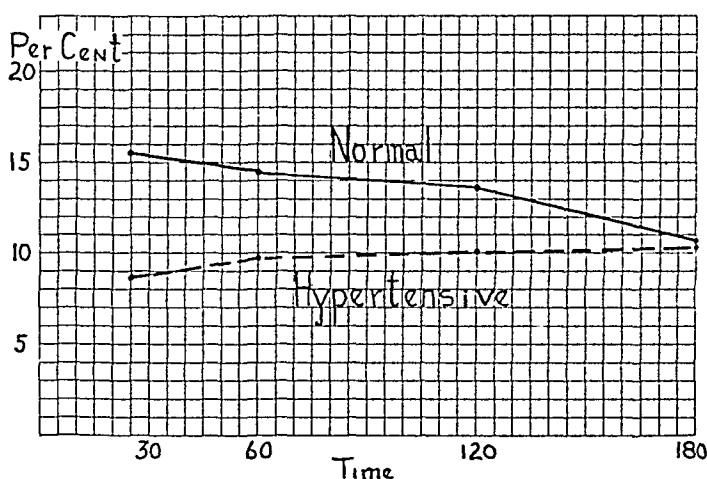


Chart 5—Percentages of ferrocyanide excreted by normal and by hypertensive patients (means), "corrected" on the basis of the ferrocyanide remaining within the body.

Before considering the probable significance and interpretation of these observations on renal function in hypertensive disease of the arteries, one must point out that these data were obtained from patients with so-called "essential hypertension," with little or no evidence of renal injury. Patients with obvious nephritis and "secondary hypertension" and those with long-standing hypertensive arteriosclerosis with nephrosclerotic changes were rigidly ruled out as not representing the entity under consideration¹⁴. Efforts to find some correlation between the levels of arterial tension and the excretion of ferrocyanide were unavailing. No such correlation could be elicited in relation to the

¹⁴ Stieglitz, E. J. (a) Arterial Hypertension, New York, Paul B. Hoeber, Inc., 1930, (b) Abnormal Arterial Tension, New York, National Medical Book Company, 1935, (c) J. Michigan M. Soc. **34**: 70 (Feb.) 1935.

systolic or the diastolic tensions or the pulse pressures in individual patients or in groups of patients. In the series studied the systolic tensions ranged from 130 to 250 mm of mercury, the diastolic tensions from 90 to 170 mm and the pulse pressures from 35 to 105 mm. There was no relation between the ferrocyanide output and age. In all but a few instances the urine was clinically free of protein, although occasional hyaline and/or granular casts were frequently observed. In many instances the only evidence of renal injury was revealed by the test for impaired glomerular function with sodium ferrocyanide.

What is the significance of the conspicuous delay in elimination of ferrocyanide in hypertensive arterial disease and the almost uniform rate of excretion throughout the three hours of the test? In view of the present knowledge of the mechanisms of renal excretion,^{14b} a tentative conclusion becomes obvious. Apparently, hypertensive disease of the arteries distinctly impairs the capacity of the glomeruli to respond to increased effort. Excretion of sodium ferrocyanide is a test for glomerular efficiency. The excretion of this salt is delayed and impaired in hypertension even though the urine may be apparently normal. Throughout the period of elimination studies, the percentage of salt excreted in relation to that remaining in the body is almost the same. This is most suggestive that in hypertensive disease the glomeruli are working at or near the maximum of their capacity all the time. That such impairment is revealed more readily and more clearly by tests with sodium ferrocyanide than by those with phenol-sulfonphthalein and/or urea in the early stages of hypertensive disease is to be expected when one recalls the evidence demonstrating that ferrocyanide salts are eliminated wholly or almost wholly via the glomeruli whereas phenolsulfonphthalein¹⁵ and urea likewise, in part,¹⁶ are secreted by the proximal convoluted tubules. Injury to the glomeruli interferes with filtration and excretion more than with the free flow of blood.¹⁷ The presence or absence of proteinuria is no criterion of the functional capacity of the kidneys. This view accords with the results of the epoch-making investigations of Goldblatt and his co-workers on the production of experimental hypertension by interference with the renal circulation.¹⁸ Thus the present observations give further, clinical evidence that the glomeruli are vitally important factors in the pathogenesis of hypertensive arterial disease. The concept that glomerular elimination of water is impaired has been suggested as an etiologic mechanism in hypertension, but it appears

15 Potter, A. C., and Bell, E. T. *Am J M Sc* **149** 236, 1915.

16 Stieglitz, E. J. *M Clin North America* **21** 281 (Jan.) 1937, footnote 14 b.

17 Weiss, S., Parker, F., Jr., and Robb, G. P. *Ann Int Med* **6** 1599 (June) 1933.

18 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. *J Exper Med* **59** 347 (March) 1934.

far more logical to presume impairment in the elimination of some solute or solutes whose normal route of excretion, like that of ferrocyanide, is via the glomeruli¹⁹

As the test of glomerular function with sodium ferrocyanide approximately parallels the response elicited with the test of urea clearance¹² and the phenolsulfonphthalein test,¹ the rates of excretion of ferrocyanide for the first half hour were compared with the maximum value obtained for the specific gravity of the urine in the concentration test. The results are shown in chart 6. The routine of Fishberg²⁰ was employed for the concentration test, as it has yielded the most consistently satisfactory results with a maximum of simplicity in the procedure.²¹ The renal concentration test is unquestionably considered

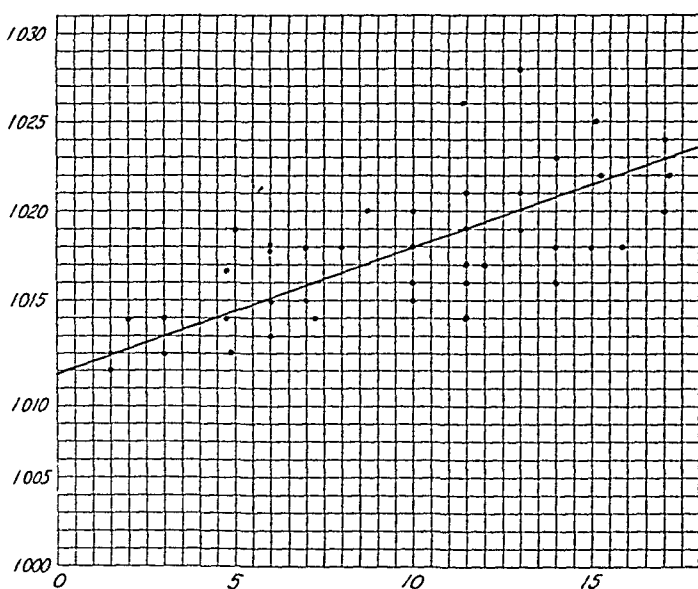


Chart 6—Relation of the test of glomerular function to the maximum value for specific gravity obtained by concentration tests, ferrocyanide output during the first half-hour in terms of percentages of the injected dose

the most sensitive indicator of early depreciation of the renal reserve, for it creates conditions of stress. It is physiologic, simple, safe and informative, and, although it measures primarily tubular effectiveness in concentrating the urine, it must be emphasized that functional impairment of the kidney *always involves both the tubules and the glomeruli*.²⁰ Glomerular injury inevitably impairs the tubular blood supply, tubular injury can come only via the blood stream, which has traversed the glomerular tufts before reaching the tubules. Thus it is

19 Stieglitz¹⁶ Goldblatt, Lynch, Hanzal and Summerville¹⁸

20 Fishberg, A. M. Urinary Nature of the Impairment of Renal Function, Arch Int Med **38** 259 (Aug.) 1926, Hypertension and Nephritis, ed 2, Philadelphia, Lea & Febiger, 1934

21 Stieglitz (footnotes 14 a and b and 16)

truly impossible that either "pure" glomerular nephritis or "pure" tubular nephrosis exists, the functional impairment is always mixed, although the injury to one or the other structure may predominate. Thus, despite the fact that excretion of sodium ferrocyanide may be taken as a measure of glomerular efficiency, there should be and is a fairly close parallelism between the response elicited with all the tests of renal function.

As has been noted, the greatest deviation from the normal excretion of ferrocyanide occurs in the first hour after injection not only in hypertensive arterial disease but in acute and in chronic nephritis as well. It is therefore possible to shorten the procedure and analyze only specimens obtained thirty and sixty minutes after the injection, omitting the specimens at one hundred and twenty and one hundred and eighty minutes. For routine clinical purposes, especially with ambulatory patients, this shortening of the time required has been found entirely satisfactory. In prenatal evaluation of renal function²² it is particularly appreciated by the patients, and there is no loss in the informativeness of the results. In a considerable but uncompleted series of prenatal observations the one hour application of the sodium ferrocyanide test has been useful warning of renal injury in a number of cases.

CONCLUSIONS

The essential criteria of a practical functional test of clinical value are simplicity, safety, specificity for the structure or function studied, creation of stress and relative uniformity of normal findings. The test of glomerular function with sodium ferrocyanide fulfils these criteria. But so do other tests. What then, if any, are the advantages offered by this method of measuring renal efficiency? Other than the far more cumbersome and technically difficult studies of creatinine or inulin clearance, the ferrocyanide test is thus far the only clinical method of specifically measuring the excretory activity of the glomeruli. The general utility of the test is attested by the parallelism of the responses to those elicited with the renal concentration test, the urea clearance studies and the phenolsulfonphthalein test. The rate of excretion is unaffected by the volume of urine secreted. In certain conditions of glomerular injury, as in the notable example of hypertensive arterial disease, the test of glomerular function reveals otherwise hidden impairment. In the present investigations it has been shown that in hypertensive disease without other evidence of renal injury the rates of excretion of ferrocyanide take on a characteristic form which implies definite change in the ability of the glomeruli to excrete solutes. These observations not only are compatible with but lend support to the con-

²² Stieglitz, E. J. *Obstetric Medicine*, edited by F. L. Adair and E. J. Stieglitz, Philadelphia, Lea & Febiger, 1930, chap. 28.

cept that a primary initiating factor in the pathogenesis of hypertensive disease may be glomerular impairment. Further studies along these lines are needed and are contemplated.

The test is not applicable in cases of urinary obstruction due to prostatic hypertrophy and/or with urethral lesions, because of the urethral irritation set up. Utilization of the test in prenatal study offers specific advantages in the detection of lowered renal reserve, particularly in the discovery of preexistent hypertension and/or nephritis.²²

SUMMARY

Sodium ferrocyanide, being excreted by the glomeruli, may be safely used as a test substance for determining glomerular efficiency.

The procedure found most applicable is the intravenous injection of 0.5 Gm of the hydrated salt (representing 0.25 Gm of the anhydrous salt) freshly dissolved in 10 cc of sterile distilled water, specimens of urine are collected thirty, sixty, one hundred and twenty and one hundred and eighty minutes after injection and their ferrocyanide content determined. For ambulatory patients analysis of the first two specimens suffices. Caution must be employed in that the solution *must* be clear before the injection is made.

The excretion rate of ferrocyanide approximately parallels the results obtained with the urea clearance test, the phenolsulfonphthalein test and the renal concentration test.

Extension of the control series of patients with apparently normal renal function has further clarified what constitutes a normal response. The range of variation is not excessive (chart 1).

Calculating the rates of excretion on the basis of the ferrocyanide remaining within the body rather than the total dose of salt reveals that the rate of excretion is remarkably uniform throughout the period of study (chart 2).

In hypertensive arterial disease without other evidence of nephritis the glomerular function is early and clearly impaired. This depression is most conspicuously manifest during the first hour of excretion. The curve of the percentages of excretion in hypertensive disease is characteristic (chart 5) and suggests that occult glomerular injury depreciates the capacity of the glomeruli to excrete certain solutes promptly. The etiologic relations of these phenomena to hypertensive disease are briefly considered.

The final evaluation of the usefulness and clinical applicability of the test of glomerular function with sodium ferrocyanide can come only after extended investigation, but the present report clearly confirms the impressions gained in the preliminary studies and emphasizes its potential value in clinical study of the relation of glomerular injury to hypertensive disease.

RENAL FUNCTION AND THE NUMBER OF GLOMERULI IN THE HUMAN KIDNEY

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The majority of tests of renal function are interpreted and their results recorded in terms of the values obtained for normal persons. Any one of them yields an estimate of the efficiency of the kidneys at a particular time, but this may be of little prognostic significance, for it is well known that in acute nephritis, acute infections, ureteral obstruction or cardiac failure renal function may be severely depressed and yet with recovery of the patient may return to normal. In chronic renal disease, however, decreasing functional values usually indicate the relentless progress of the condition.

The ideal test of function would give not only an estimate of the degree of loss of renal efficiency but information as to the manner in which the normal physiologic processes have been disturbed. The processes involved in the formation of urine are so complex that no test has been devised by which it is possible satisfactorily to separate interference with glomerular function and interference with tubular function. Efforts to translate the results of tests of renal function into terms of renal physiology are, however, by no means new. From a comparison of urea clearance values and autopsy observations Van Slyke and his co-workers¹ suggested that in cases of hemorrhagic and degenerative nephritis this test is a measure of the number of intact glomeruli still functioning, while in cases of arteriosclerotic nephritis it is proportional

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A preliminary report of some of these observations was presented at the Fifty-Second Session of the Association of American Physicians, May 5, 1937 (Tr A Am Physicians 52:182, 1937)

1 Van Slyke, D D, Rhoads, C P, Hiller, A, and Alving, A S. Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption, and Diuresis. The Mechanism of Urea Excretion, Am J Physiol 109:336 (Aug) 1934

to the decrease in renal blood flow. In both hemorrhagic and arteriosclerotic Bright's disease there is a marked reduction in the number of glomeruli.² The extent of such reduction may be difficult to judge from histologic sections, since the scars of destroyed glomeruli disappear without leaving recognizable traces. Taylor and his co-workers³ presented evidence, based on studies of animals of various sizes, that the "urea ratio," a value derived in a manner similar to that in which the maximum clearance is determined, can be interpreted as a measure of the mass of functioning renal tissue. It is decreased after unilateral nephrectomy and increases again with compensatory hypertrophy of the remaining kidney. This interpretation offers difficulties in cases of temporary depression of function if it is asked what part of the renal mass has ceased to function. In rabbits poisoned with a uranium compound Watanabe, Oliver and Addis⁴ grouped the lesions as mild, moderate and severe and found the urea ratio correspondingly depressed. This has been interpreted by others⁵ to mean that the ratio is a measure of the mass of "functioning" renal tissue even when the total mass is not reduced. This conception of the "mass of functioning tissue" has been criticized by Cope⁶. Smith, Goldring and Chasis,⁷ on the other hand, expressed the belief that the inulin, phenol red and diodrast clearances represent measures of glomerular filtrate, "tubular excretory mass" and effective renal blood flow. Elliot and Nuzum⁸ concluded that it is difficult to interpret the results of tests of renal function in arteriosclerotic Bright's disease in terms of the actual amount of healthy renal parenchyma, a conclusion which led Schlayer⁹ years ago to turn to functional studies in an effort to learn the kind rather than the amount of renal damage.

2 Moritz, A. R., and Hayman, J. M., Jr. The Disappearance of Glomeruli in Chronic Kidney Disease, *Am J Path* **10** 505 (July) 1934.

3 Taylor, F. B., Drury, D. R., and Addis, T. The Regulation of Renal Activity. VIII. The Relation Between the Rate of Urea Excretion and the Size of the Kidneys, *Am J Physiol* **65** 55 (June) 1923.

4 Watanabe, C. K., Oliver, J., and Addis, T. Determination of the Quantity of Secreting Tissue in the Living Kidney, *J Exper Med* **28** 359 (Sept.) 1918.

5 MacKay, E. M., and Rytand, D. A. Significance of the Phenolsulphonphthalein Test of Renal Function, *Arch Int Med* **55** 131 (Jan.) 1935.

6 Cope, C. L. Rational Assessment of Renal Damage, *Lancet* **2** 799 (Oct 13) 1934.

7 Smith, H. W., Goldring, W., and Chasis, H. The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, *J Clin Investigation* **17** 263 (May) 1938.

8 Elliot, A. H., and Nuzum, F. R. Evaluation of Measures of Renal Function in Persons with Arteriosclerotic Bright's Disease, *Arch Int Med* **57** 1151 (June) 1936.

9 Schlayer, C. Neuere klinische Anschauungen über Nephritis, *Med Klin (supp)* **8** 211, 1912, cited by Watanabe, Oliver and Addis.⁴

Tests of function may be interpreted from another point of view, namely, as measures of different renal functions without regard to the physiologic processes involved. Alving and Van Slyke¹⁰ suggested that the specific gravity test determines chiefly the ability to excrete inorganic salts, while the urea clearance test measures the ability to excrete urea. Cope⁶ concluded that all clearance tests simply measure the ability to eliminate waste and that the excretion of water and chloride is too dependent on extrarenal factors to be of value.

In order to attempt to analyze in terms of renal physiology the ways in which reduction in function may be brought about, it is necessary to know not only the results of the tests and the histologic changes in the kidneys but also the number and state of the glomeruli. This report deals with a comparison of the results of two commonly used tests, the urea clearance test and the maximum specific gravity or concentration test, and of one less widely employed, the creatinine clearance test, with the histologic appearance and particularly with the number of glomeruli.

The tests were performed from a few days to several months before death. All the patients had normal or elevated blood pressure and were free from detectable edema or other evidence of heart failure at the time the tests were performed. It is believed that by this restriction patients in whom reduced function could be attributed to diminished renal blood flow have been excluded. No patient with acute glomerulonephritis (in whom histologic evidence and the results of perfusion experiments also indicated the presence of diminished renal blood flow) was included. It was not possible, however, to carry out all three tests on every patient.

Urea clearance was calculated as "maximum" clearance and recorded as the percentage of normal for the observed volume of urine, the formula derived by Dominguez¹¹ as fitted to Van Slyke's data being used. The values were not corrected for surface area, since all the patients were adults and the correction was less than the variation in clearance values from one period to another. One to six urea clearance tests, each for two one hour periods, were made for each patient. Patients unable to cooperate in complete voiding were catheterized. The urea content of the urine was determined by the urease manometric method of Van Slyke and that of the blood by the same method or by the hypobromite method.¹²

10 Alving, A. S., and Van Slyke, D. D. The Significance of Concentration and Dilution Tests in Bright's Disease, *J. Clin. Investigation* **13** 969 (Nov.) 1934.

11 Dominguez, R. On the Renal Excretion of Urea, *Am. J. Physiol.* **112** 529 (July) 1935.

12 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

Creatinine clearance was estimated by Rehberg's¹³ method after administration of 3 to 5 Gm of creatinine by mouth unless the creatinine content of the blood was above 5 mg per hundred cubic centimeters. The values are expressed directly in cubic centimeters per minute. Hayman, Halsted and Seyler¹⁴ found the average normal creatinine clearance to be 148 cc per minute by this technic.

The concentration test used was a modification of the test of Addis and Shevky¹⁵ and of Lashmet and Newburgh¹⁶. No fluid was allowed from 10 p. m. one evening until 7 a. m. thirty-three hours later, and the specific gravity of the urine passed during the last twelve hours of the test was determined. During the day of the test the diet recommended by Lashmet and Newburgh was used. This is palatable and adequate and diminishes thirst. It was not possible, however, to carry out this rigid regimen with all patients. In some cases twenty-four or twelve hours without fluids was all that could be reasonably asked. The thirty-three hour tests and the others are indicated by different symbols in the charts. Values for specific gravity were determined by means of a Westphal balance at 20°/4° with a calibrated plummet. All values for specific gravity were corrected for protein. This was determined by Shevky and Stafford's¹⁷ method after calibration of the volume of precipitate by macro-Kjeldahl analyses.

Kidneys were obtained as soon after death as possible and perfused first with salt solution to wash out the blood and then with a mixture of ferric ammonium citrate and potassium ferrocyanide. The number of glomeruli per kidney was estimated by Kunkel's¹⁸ method, with the modification that several blocks were cut before digestion, and the completeness of injection was estimated from counts of injected and apparently patent but noninjected glomeruli in sections. This permitted the estimate from the count to be corrected for the uninjected and therefore uncounted glomeruli. Except when there were gross infarcts, the distribution of uninjected glomeruli was usually fairly uniform. One

13 Rehberg, P. B. Ueber die Bestimmung der Menge des Glomerulusfiltrats mittels Kreatinin als Nierenfunktionsprüfung, *Zentralbl. f. inn. Med.* **1** 367 (April) 1929.

14 Hayman, J. M., Jr., Halsted, J. A., and Seyler, L. E. A Comparison of the Creatinine and Urea Clearance Tests of Kidney Function, *J. Clin. Investigation* **12** 861 (Sept.) 1933.

15 Addis, T., and Shevky, M. C. A Test of the Capacity of the Kidney to Produce a Urine of High Specific Gravity, *Arch. Int. Med.* **30** 559 (Nov.) 1922.

16 Lashmet, F. H., and Newburgh, L. H. Improved Concentration Test of Renal Function, *J. A. M. A.* **99** 1396 (Oct. 22) 1932.

17 Shevky, M. C., and Stafford, D. D. A Clinical Method for the Estimation of Protein in Urine and Other Body Fluids, *Arch. Int. Med.* **32** 222 (Aug.) 1923.

18 Kunkel, P. A. The Number and Size of the Glomeruli in the Kidneys of Several Mammals, *Bull. Johns Hopkins Hosp.* **47** 285 (Nov.) 1930.

kidney from each patient was perfused, the other being subjected to the usual histologic examinations. Specimens in which there was a marked difference in weight or gross appearance of the two kidneys were discarded. Many other specimens were discarded because of failure to get good injection of the kidney. The two kidneys of a normal animal (rat,¹⁹ rabbit²⁰ and man²¹) contain approximately the same number of glomeruli. The average in the normal human kidney is about 1,250,000.

Seventy-nine patients were studied. Nineteen showed no evidence of renal disease during life, and no change or only slight change was found in the kidneys on histologic examination. These patients constituted a control group. The causes of death for this group were: military tuberculosis, 7; pneumonia, 4; a malignant process, 2; and lymphatic leukemia, duodenal ulcer, endocarditis lenta, Hodgkin's disease, coronary thrombosis and cerebral hemorrhage, 1 each. Urea clearance was determined for 16 patients in this group, creatinine clearance for 15 and specific gravity for 11. There were 2 patients with subacute and 7 with chronic glomerulonephritis. Urea clearance was determined for 8, creatinine clearance for 6 and specific gravity for 7. Thirty-nine patients had arteriolar nephrosclerosis of varying degree. Urea clearance was determined for 34, creatinine clearance for 31 and specific gravity for 29. Twelve patients had low renal function during life, but on postmortem examination only cloudy swelling or "bile nephrosis" and a normal number of glomeruli were found. Urea and creatinine clearances were determined for all of this group, specific gravity for only 3.

The patients showing reduced values for renal function may be divided into two groups: (1) those with chronic renal disease, either inflammatory or vascular, but without clinical evidence of acute infection, and (2) those with acute infections (typhoid, pneumonia), septicemia or obstructive jaundice but without chronic Bright's disease. The mechanism for the reduction in function in these two groups may be considered separately. The same 19 "normal" patients have been used as controls for both groups.

CHRONIC BRIGHT'S DISEASE (INFLAMMATORY AND VASCULAR)

When the mean creatinine or urea clearance is plotted against renal weight the correlation is extremely poor (chart 1). While in this study patients with kidneys weighing less than 100 Gm. each always showed

19 Arataki, M. On the Postnatal Growth of the Kidney with Special Reference to the Number and Size of the Glomeruli, *Am J Anat* **36**:399 (Sept.) 1926.

20 Hayman, J. M., Jr., and Starr, I. Experiments on the Glomerular Distribution of Blood in the Mammalian Kidney, *J. Exper. Med.* **42**: 641 (Nov.) 1925.

21 Moore, R. A. The Total Number of Glomeruli in the Normal Human Kidney, *Anat. Rec.* **48**: 153 (Jan.) 1931.

reduced clearance, extremely low clearance was always encountered in patients whose kidneys weighed 150 to 200 Gm each. With kidneys weighing 100 to 175 Gm each, the clearance values showed no correlation with renal weight. Nor in this adult population is the correlation any better if clearance is plotted against renal weight per square meter of body surface.²²

This lack of correlation between clearance values and renal mass is in sharp contrast to Addis' and MacKay's data on normal animals and man. The size of the kidney, however, is no good measure of the

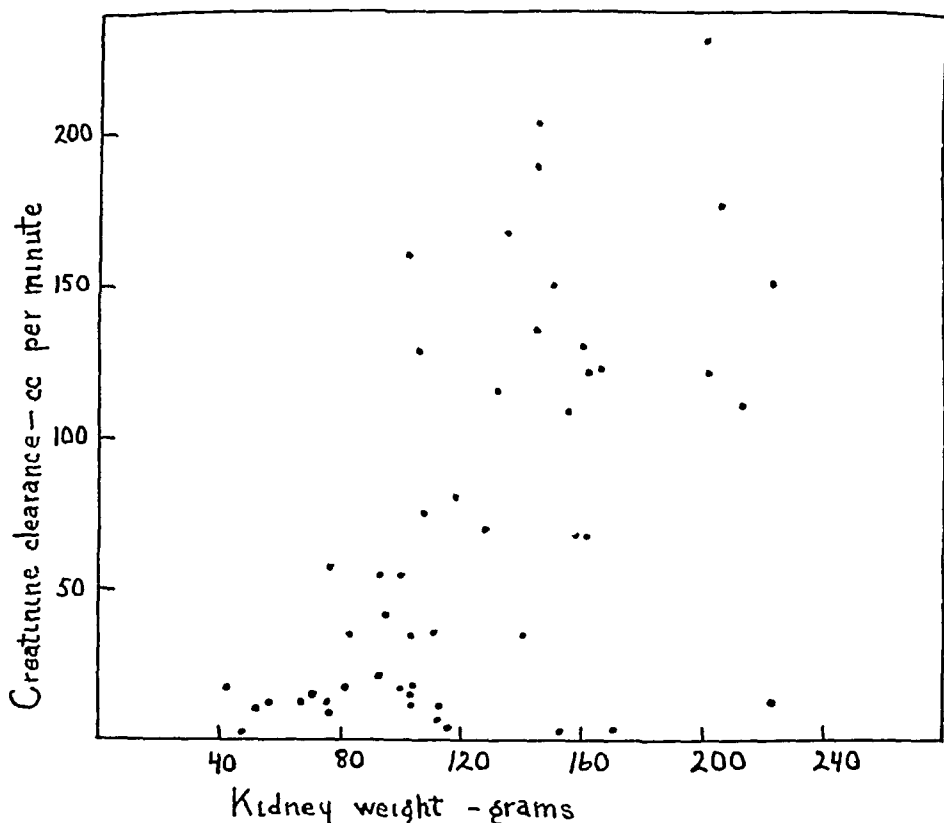


Chart 1—Relation of average creatinine clearance and renal weight

number of glomeruli it contains. Not only does the infant kidney have as many glomeruli as the adult kidney, but a relatively small pathologic adult kidney may have a fairly large number of glomeruli, while a kidney of approximately normal size, if it contains much scar tissue, may give a low count.

If, however, the mean urea or creatinine clearance value is plotted against the number of glomeruli per kidney, a reduction in clearance

²² MacKay, E. M. Kidney Weight, Body Size and Renal Function, *Arch Int Med* 50:590 (Oct) 1932.

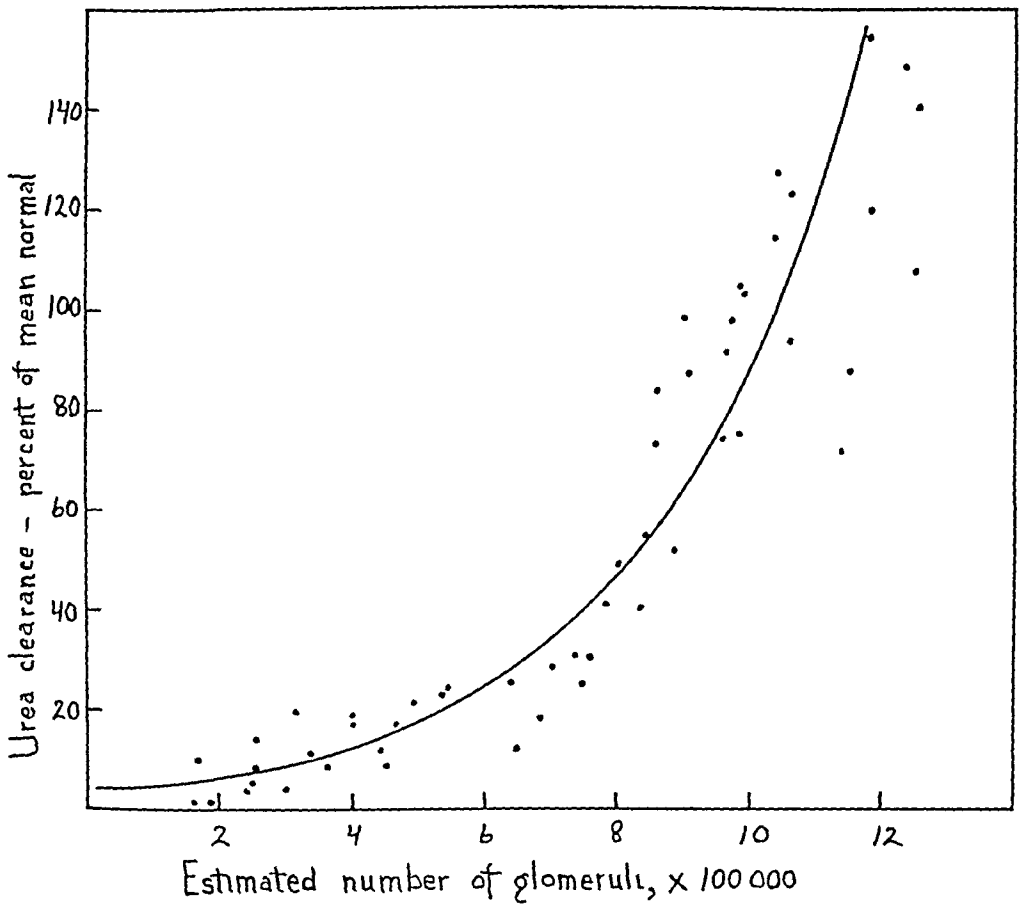
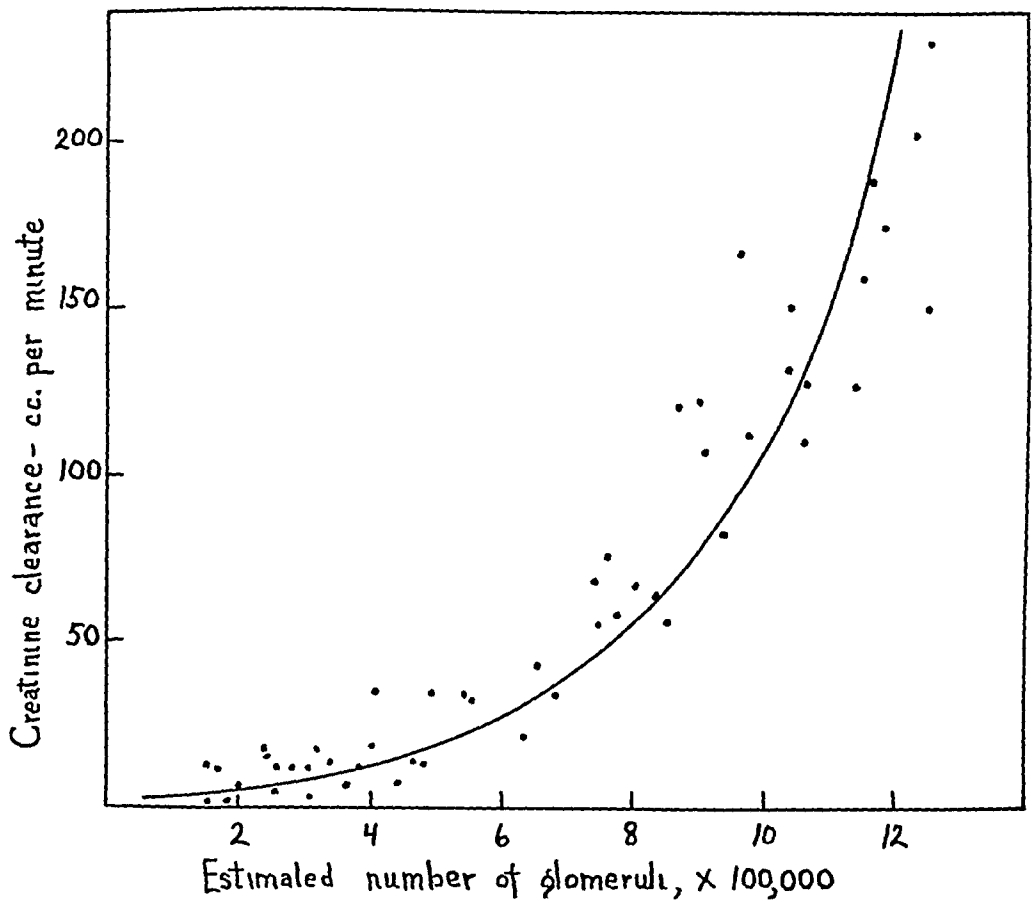


Chart 2—Relation between creatinine and urea clearance and the estimated number of glomeruli per kidney in patients without evidence of renal disease and patients with chronic Bright's disease

with a decreasing number of nephrons is apparent (chart 2). The relation, however, is not direct, clearance being reduced more rapidly than the number of nephrons. There is considerable scattering, but the points fall fairly well along an exponential curve. The curve of best fit has been calculated by the method of least squares. The curves for urea and for creatinine clearance are almost the same. The equation for creatinine is $Y = 3.186e^{0.00357X}$ and for urea $Y = 3.549e^{0.00322X}$, in which Y represents the clearance in cubic centimeters per minute for creatinine and in per cent of mean normal for urea, and X the estimated number of glomeruli per kidney. These equations are merely empiric correlations of observed data and obviously have no physiologic significance. This agrees with Hayman, Halsted and Seyler's conclusion that in chronic Bright's disease the percentage reduction below normal of urea and creatinine clearance is approximately the same.

In dogs in which the renal mass has been reduced by subtotal nephrectomy the percentage reduction in clearance is less than the reduction in glomeruli, so that the curve is convex upward.²³ In addition, the reduction in urea clearance is somewhat less than in creatinine clearance until the number of remaining glomeruli is extremely small. In these dogs two factors apparently contributed to the disproportionately large clearance in relation to renal mass. Glomerular counts include all glomeruli and are not necessarily a measure of the number through which blood was flowing or which were "active" when the clearance was determined. With moderate reduction in the number of glomeruli, it seems reasonable to suppose that all or the greater number of those which remain will be continuously active.²⁴ When renal mass has been reduced to a point where retention of nitrogen begins, it seems reasonable to suppose that all of the remaining glomeruli will be continuously open and that the relatively high clearance for the number of remaining glomeruli is attributable to a greater blood flow per glomerulus than occurs in the normal kidney.

Similar reasons may be advanced for the proportionately smaller reduction in clearance in relation to the number of glomeruli in the human kidney after unilateral nephrectomy. Contrary to the common belief that, owing to compensatory hypertrophy, renal function is normal after removal of half the renal mass, analysis of data presented by Ellis and Weiss²⁵ and similar data from this laboratory indicate that there is

23 Hayman, J. M., Jr., Shumway, N. P., Dumke, P., and Miller, M. Experimental Hyposthenuria, *J. Clin. Investigation* **18** 195 (March) 1939.

24 Moore, R. A., and Lukianoff, G. F. The Effect of Unilateral Nephrectomy on the Total Number of Open Glomeruli in the Rabbit, *J. Exper. Med.* **50** 227 (Aug.) 1929.

25 Ellis, L. B., and Weiss, S. The Renal Function in Persons with One Kidney, *Am. J. M. Sc.* **186** 242 (Aug.) 1933.

a significant reduction in the mean creatinine and urea clearance²⁶ The reduction, however, is not proportional to the reduction in renal mass but is similar in degree to that found in experimental animals

While in experimental animals subjected to subtotal nephrectomy the remaining glomeruli are supposedly normal, those in human kidneys which are the seat of chronic Bright's disease are not Consequently, the area of filtering surface will be reduced more than the number of glomeruli By the method of counting, however, this was neglected, since a glomerulus which contained any dye was included In an effort to correct for this defect Dr A R Moritz and Dr William Wartman of the staff of the Institute of Pathology studied sections of these kidneys and made an estimate of the degree of damage in from 100 to 200 consecutive glomeruli Without knowledge of the results of the functional tests or of the glomerular counts, they grouped the glomeruli according to their appearance in the histologic sections into four categories, depending on whether they appeared to be normal or to be slightly, moderately or severely damaged If it is assumed that the glomeruli in these four groups had, for instance, 100, 75, 50 and 25 per cent of the filtering surface of normal glomeruli, it is possible to derive a figure from the observed glomerular count which perhaps gives a closer approximation to the actual filtering area With these figures, which are expressed in terms of an equivalent number of normal glomeruli, the plot of clearance against the calculated equivalent number of normal glomeruli still follows a curve which is convex downward, although less markedly so than when the observed number of glomeruli is used If, however, it is assumed that the area of filtering surface in the four groups approximated 100, 50, 25 and 10 per cent of normal, the curves more nearly approach a straight line (chart 3) Such assumptions and calculations are, of course, purely arbitrary and in themselves are of no significance They do, however, suggest that physiologic impairment in a glomerulus may be much greater than the degree of damage estimated from histologic sections The fact that the rate of reduction in

26 Ellis and Weiss determined the renal function of 9 patients who had had a nephrectomy for tumor, stone or pyelonephrosis and who showed a normal blood pressure and no complications Their figure for the mean creatinine clearance of normal persons was 151 cc, with a standard deviation of 13.6 cc, while the mean creatinine clearance for these apparently normal persons with one kidney was 114.0 ± 13.1 cc The difference in the means of 37.0 ± 4.2 cc is significant We have examined 11 similar patients with one kidney The mean creatinine clearance was 100.5 ± 3.4 , which also differs significantly from the mean of 148 ± 3.4 obtained for normal persons by Hayman, Halsted and Seyler (difference of means equals 48 ± 4.6 cc)

clearance in relation to the number of glomeruli falls more rapidly in chronic Bright's disease than after unilateral nephrectomy in man or subtotal nephrectomy in experimental animals is indirect evidence of a fundamental difference between the two processes. In the one the remaining nephrons are normal, in the other pathologic. The pathologic changes may include not only a reduction in area of filtering surface but a decrease in the permeability of the glomerular membrane, so that there is less filtrate for a given filtering area and capillary pressure. This is perhaps brought out more clearly if the average creatinine

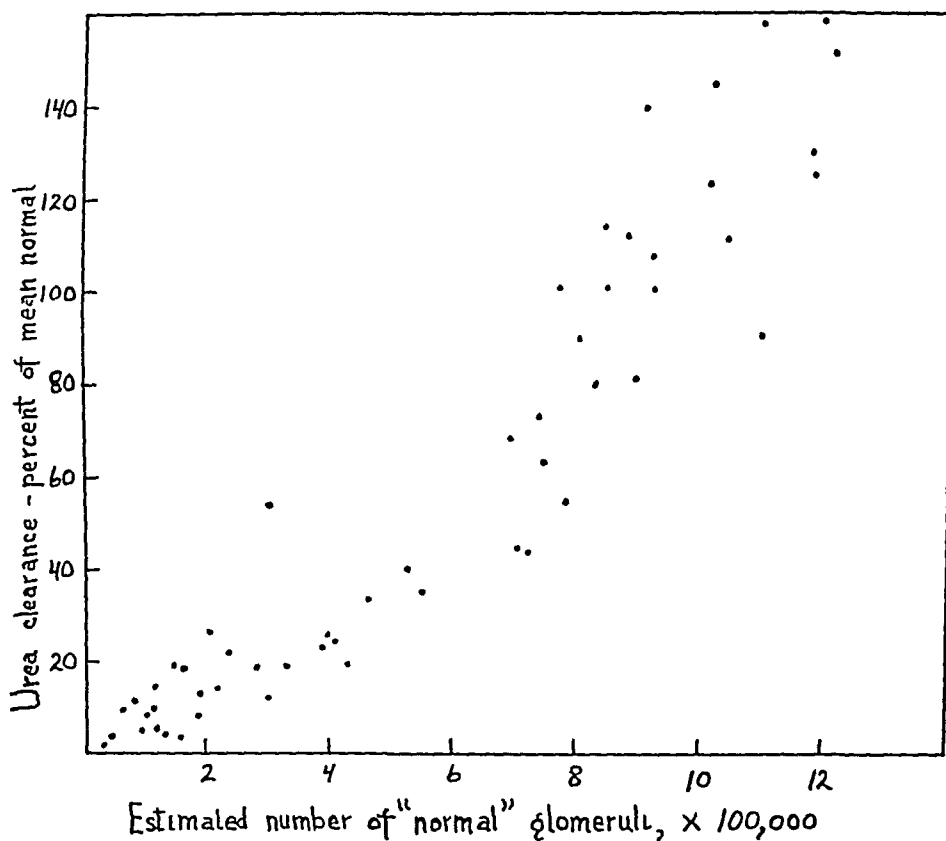


Chart 3—Relation between urea clearance and the estimated number of "normal" glomeruli on the assumption that histologic grading represented 100, 50, 25 and 10 per cent of the normal filtering surface

clearance per hundred thousand glomeruli is calculated. With two normal kidneys, if all the glomeruli are active this is about 5.9 cc per hundred thousand, and with 700,000 glomeruli per kidney, about 2.9 cc. When the glomeruli are reduced to 200,000 per kidney the average clearance is only 1 cc per hundred thousand. Comparable figures are obtained for urea clearance. The disproportionate reduction in clearance could, of course, also be accounted for if the tubule cells of the

remaining nephrons in these kidneys were damaged so that secretion of creatinine was reduced and back diffusion of urea increased to the same degree. There is nothing in these data to suggest that the aglomerular tubules in such kidneys described by Oliver and Luey²⁷ and by MacNider,²⁸ are functionally significant, at least in the elimination of urea and creatinine.

The concentration test is a sensitive, reliable and easily performed test of renal function, but it is well known that the specific gravity may reach a minimum value of about 1.010 while the patient is still free from

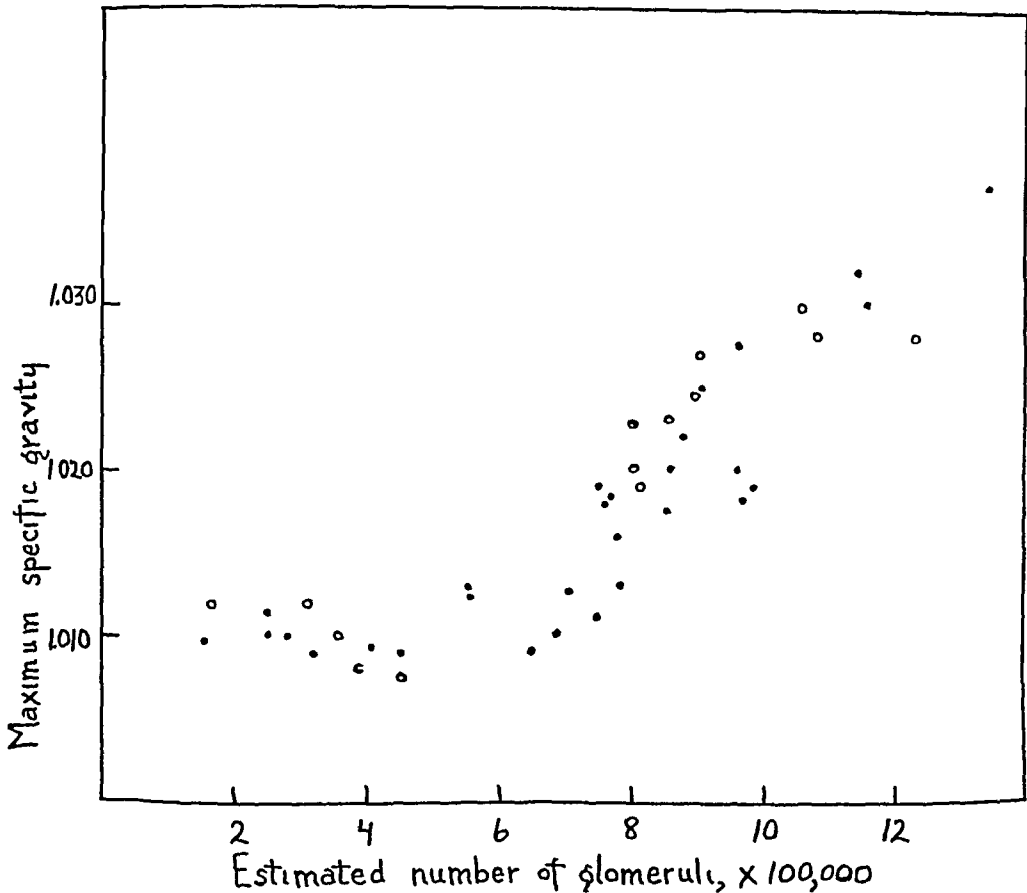


Chart 4—Relation between the maximum specific gravity and the number of glomeruli per kidney in patients without evidence of renal disease and patients with chronic Bright's disease. The circles represent thirty-three hour concentration tests, the dots, those after shorter periods of abstinence from fluids.

symptoms and that with further progress of the disease no further reduction in specific gravity occurs. Alving and Van Slyke compared

27 Oliver, J, and Luey, A. S. Plastic Studies in Abnormal Renal Architecture. Aglomerular Nephrons of Terminal Hemorrhagic Bright's Disease, *Arch Path* **19** 1 (Jan) 1935.

28 MacNider, W. deB. Pathological Changes in the Dog Kidney Resembling Normal Histological Structure in the Aglomerular Fish Kidney, *Opsanus Tau*, *Proc Soc Exper Biol & Med* **31** 293 (Nov) 1933.

the urea clearance and concentration tests and found that both were equally good until the specific gravity had fallen to 1.010, which occurred when the value for urea clearance had reached about 35 per cent of the average normal. After this the clearance test alone showed the progress of the disease.

These facts are confirmed by a correlation of the maximum specific gravity and the number of glomeruli (chart 4). The shape of the curve is different from that afforded by a correlation of the clearance value and the number of glomeruli. It is approximately a horizontal line up to between 700,000 and 800,000 glomeruli per kidney and then rises at an angle of 45 degrees to the normal range. The point of apparent discontinuity, about 700,000 or 800,000 glomeruli per kidney, corresponds to about 35 per cent of normal urea or creatinine clearance on the other curve. The reason for the distribution in this scatter diagram invites speculation. Van Slyke and his associates²⁹ found that the urea clearance was reduced to 40 per cent of the mean normal before there was any retention of urea. These data include only 4 patients with glomerular counts above 800,000 in whom the urea nitrogen content of the blood was above 20 mg per hundred cubic centimeters, and the counts for all 4 of these were between 800,000 and 900,000. Only 2 patients with counts below 800,000 had a urea nitrogen content below 20 mg per hundred cubic centimeters and only 4 below 30 mg, and the glomerular counts of these patients all ranged about 700,000. The inference seems strong that the apparent discontinuity corresponds to the point at which all of the remaining glomeruli become continuously active. The general shape of the scatter diagram is not changed if the maximum value for specific gravity is plotted against an equivalent number of "normal" glomeruli as described. The point of discontinuity then corresponds to about 400,000 to 500,000 glomeruli per kidney, which again corresponds roughly with a urea clearance of 35 per cent if one assumes that the area of filtering surface in the normal, slightly damaged, moderately damaged and severely damaged glomerulus is 100, 50, 25 and 10 per cent of that in a normal glomerulus.

There is little correlation between the systolic blood pressure and the estimated number of glomeruli, except that no patient was encountered with less than 700,000 glomeruli per kidney who had a systolic pressure below 150 mm of mercury (chart 5). On the other hand, a

²⁹ Van Slyke, D. D., McIntosh, J. F., Moller, E., Hannon, R. R., and Johnston, C. Studies of Urea Excretion. VI. Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, *J. Clin. Investigation* 8: 357 (April) 1930.

person with a normal number of injectable glomeruli per kidney may have an elevated blood pressure. Below 700,000 glomeruli per kidney there was no correlation between the number of injectable glomeruli and the degree of elevation of blood pressure. Of the 7 patients with a glomerular count above 800,000 and a systolic blood pressure above 140 mm, all but 1 excreted urine with a specific gravity above 1.020 as ascertained by the concentration test, and this one showed a gravity of 1.019. While this may be a coincidence and dependent on the small

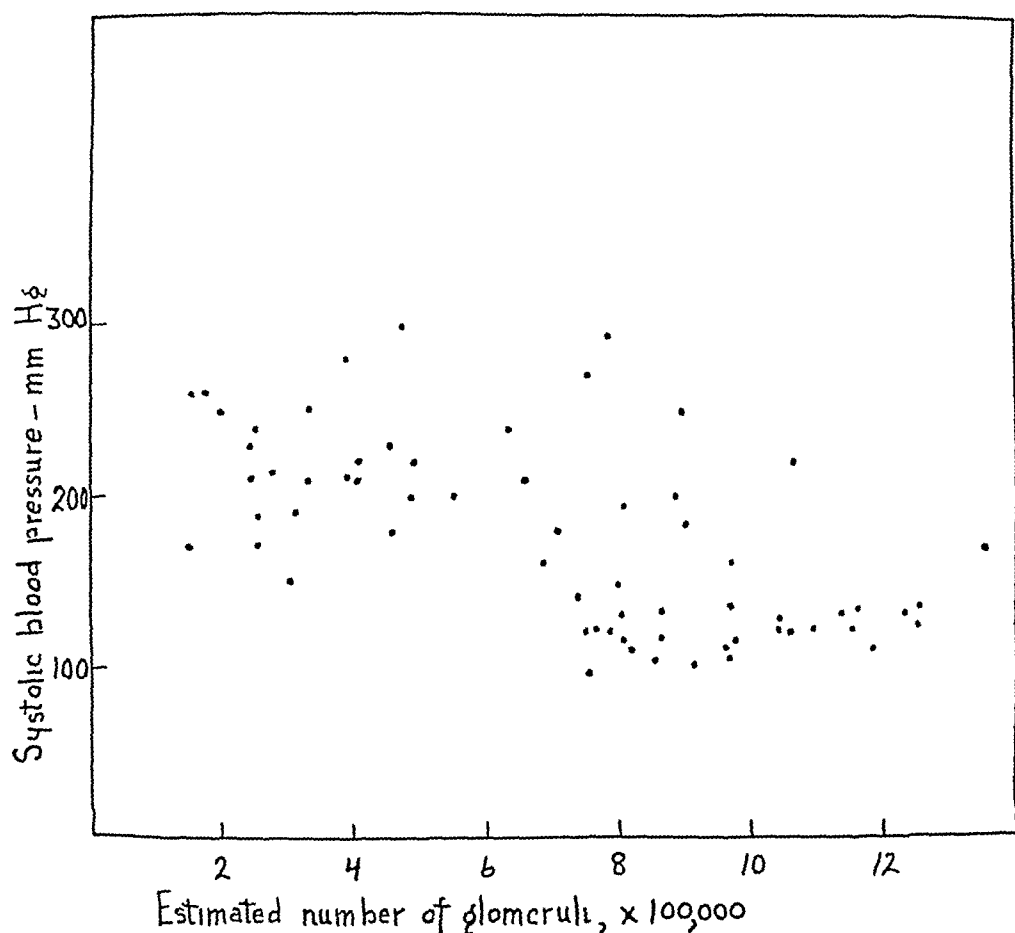


Chart 5—Relation between the systolic blood pressure and the number of glomeruli per kidney

number of observations, the data at hand at least suggest that when the glomeruli have been reduced to 700,000 or 800,000 per kidney there is some change associated with the presence of elevated blood pressure and loss of concentrating power. It does not follow, however, that these are causally related, for dogs in which Goldblatt and his co-workers³⁰ had produced marked persistent hypertension by constriction of the

30 Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. Studies on Experimental Hypertension, *J. Exper. Med.* 59:347 (March) 1934.

renal arteries retained a normal concentrating power, and some dogs in which hyposthenuria had been produced by subtotal nephrectomy showed no significant rise in blood pressure ²³

TOXIC NEPHROSES

Dogs poisoned with uranium acetate showed marked reduction in clearance and inability to concentrate their urine in spite of a normal number of glomeruli and a normal blood pressure and renal blood flow ²³ This is most readily attributed to damage to the tubule cells, which

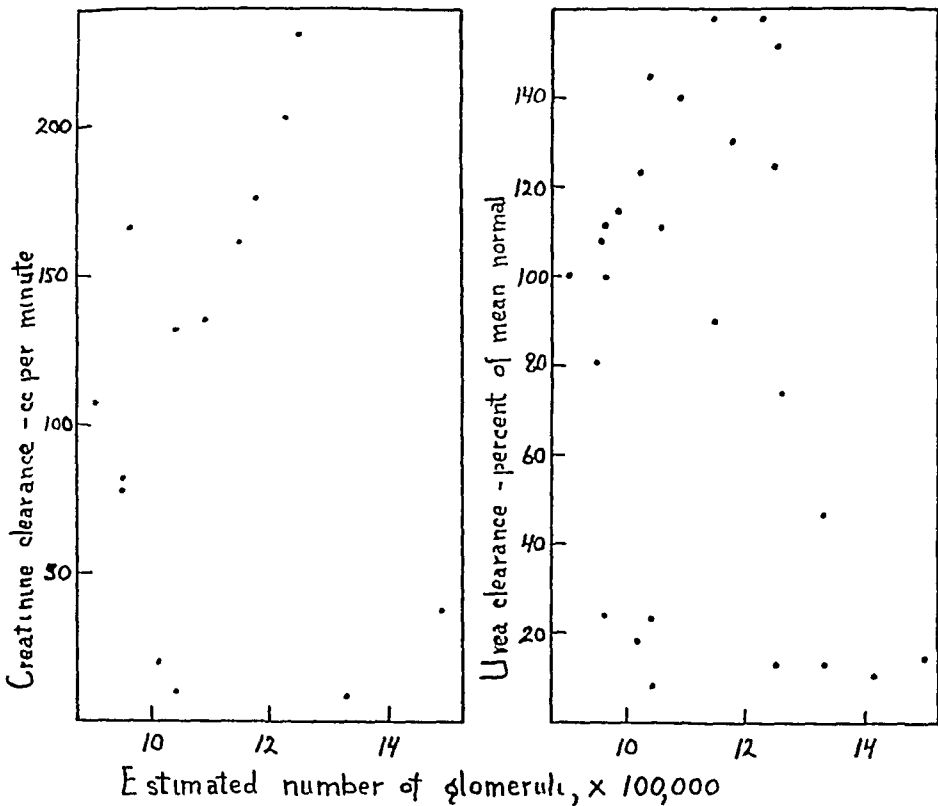


Chart 6—Relation between creatinine and urea clearance and the estimated number of glomeruli per kidney in patients without evidence of renal disease and patients with toxic nephroses

interferes with the reabsorption of water and at the same time permits more back diffusion not only of urea but of creatinine. Similarly, some patients with such acute infections as pneumonia and typhoid or with miliary tuberculosis, septicemia or jaundice show markedly reduced clearance in spite of a normal number of glomeruli which histologically show little or no damage and a normal blood pressure (chart 6). If the patient recovers from the original disease the clearance returns toward normal.

Data on concentrating power are lacking because withholding fluids for a long period was not justified. In chronic renal disease the specific gravity of the urine just before death is usually at least as high as that obtained with a concentration test, provided an infusion has not been given recently. If such specimens represent approximately maximal concentrating ability, then such data as are available indicate that these patients are unable to excrete a urine of normally high specific gravity.

It is, of course, obvious that a combination of these two mechanisms, reduction in the number of nephrons and tubular damage, leading to low clearance may occur. When a patient with chronic renal disease suffers an acute infection or a ureteral obstruction, clearance may suddenly be markedly reduced and may then return toward the previous level when the infection or other cause of depression disappears. Other mechanisms causing low clearance may be diminished renal blood flow or an inadequate pressure in the glomerular capillaries. The former may occur in acute nephritis and in cardiac failure, the latter, in shock, hemorrhage or Addison's disease. Patients in whom any of these conditions (or combinations of them) were present have, as far as possible, been excluded from this study.

SUMMARY

Creatinine and urea clearance, maximum urinary specific gravity and blood pressure were correlated with the number of glomeruli per kidney, estimated after postmortem perfusion, in patients with and in patients without disease of the kidneys.

In chronic glomerulonephritis and nephrosclerosis the values for creatinine and urea clearance are closely correlated with the number of glomeruli. Maximum specific gravity falls with the decrease in the number of glomeruli until the latter reaches 700,000 to 800,000 per kidney, after which it remains fixed in spite of further reduction in the number of glomeruli. If the number of glomeruli per kidney is less than 700,000, the systolic blood pressure is invariably above 150 mm.

In certain cases of acute infections and jaundice, clearance and concentrating ability may both be markedly reduced in spite of a normal number of glomeruli showing no significant changes in histologic sections.

BACTERIAL ENDOCARDITIS

REPORT OF A CASE IN WHICH THE CAUSE WAS ACTINOMYCES BOVIS

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The clinical syndrome of subacute bacterial endocarditis occurs frequently and is today a well recognized entity. Little has been added to knowledge of the subject since Libman's publications¹. It is now well known that while *Streptococcus viridans* is the most common cause of this disease, a large variety of other bacteria may produce a similar picture. Among these are *Bacillus influenzae*, *Enterococcus*, *Meningococcus*, *Bacillus diphtheriae*, *Pneumococcus*, *Gonococcus* and organisms of the *Brucella* group. However, the occurrence of a similar clinical picture caused by higher bacteria is rare. Only 1 case—that of Jervell,² in which the condition was caused by *Leptothrix*—is to be found in the literature. For this reason, the case to be described is of unusual interest, since the causative agent of the disease was found to be *Actinomyces bovis*.

REPORT OF CASE

History—W J, a 24 year old American-born Jew, a chiropodist, was admitted to the medical service of the Hospital for Joint Diseases on Oct 16, 1936. The family history was noncontributory. The only disease he had had as a child was measles. There was no history of rheumatism, chorea or sore throats. In 1931 he had been observed at another hospital for an attack of acute epigastric pain, associated with fever and acholic stools but without jaundice (?), and had improved in a few days, without any diagnosis being made. The condition never recurred.

On Oct 5, 1936, he became ill with pain in both calves, malaise, nausea and vomiting. Thereafter for six days he had a spiking temperature of 104 F in the morning, attended by chills and sweats. For the next four days the temperature remained at an approximate level of 102 F.

From the Medical Service of the Hospital for Joint Diseases, Dr A A Epstein, Director

1 Libman, E, and Celler, H. The Etiology of Subacute Infective Endocarditis, *Am J M Sc* **140** 516, 1910. Libman, E. Cardiac Lesions of Subacute Bacterial Endocarditis, *ibid* **164** 313, 1912. The Clinical Features of Subacute *Streptococcus* (and *Influenzal*) Endocarditis in the Bacterial Stage, *M Clin North America* **11** 117, 1918. Libman, E, and Friedberg, C K. Bacterial Endocarditis, in Piersol, G M, Borty, E L, and others. *Cyclopedia of Medicine*, Philadelphia, F A Davis Company, 1932, vol 3, p 181.

2 Jervell, O. *Leptothrix* in the Blood in a Case of Malignant Endocarditis, *Norsk mag f lægevidensk* **83** 36, 1922.

Physical Examination—Examination on admission revealed an acutely ill subject with a temperature of 104 F. Respiration was normal, the skin was clear, the eyegrounds were normal and the scleras were not discolored. The heart was not demonstrably enlarged, the sounds were forceful, regular and of good quality, the rate was 120. A soft, short systolic murmur was localized at the apex. The lungs were clear. There were increased spasticity and some tenderness in the right upper quadrant of the abdomen, with tenderness on deep percussion over the lower right costal cage. The spleen was not palpable. There was no lymphadenopathy. There was no nuchal rigidity or other abnormal neurologic finding. No clubbing of the fingers or toes was noted. A tentative diagnosis of typhoid fever was made, although bacterial endocarditis was seriously considered.

Course—During the remaining three and a half weeks of the patient's life, his fever fluctuated between 103 and 104 F. The faint systolic murmur heard on admission gradually became harsher, louder and more widely transmitted. Six days after admission he began to cough and expectorate blood-streaked sputum. Dulness and diminished respiratory sounds were found at the base of the right lung. The spleen seemed enlarged on percussion but still could not be felt. The patient's general condition became steadily worse, and on the eighth day after admission petechiae were first noted in the left conjunctiva and on the left arm. At this stage the diagnosis of subacute bacterial endocarditis was made. Dr. E. Libman, who saw the patient in consultation, concurred in this diagnosis. Slight cyanosis of the lips and finger nails appeared, and fine crepitant rales now were heard at the bases of both lungs. New crops of petechiae, many of which had pale centers, appeared daily on various parts of the body. In addition, somewhat larger purpuric lesions developed first over the palms and soles and later over other parts of the body. The sensorium gradually became clouded, and on the eighteenth day the patient lapsed into a stupor, which deepened progressively. Dyspnea became marked, and the signs in the chest increased. Gangrenous areas developed on the lobe of the right ear, both heels and the left leg. Coma became deeper, signs of left hemiplegia developed, and death occurred on November 10, twenty-five days after admission.

Treatment had consisted of the usual supportive measures, in addition to two transfusions and oxygen administered by nasal catheter. In view of the nature of the organism, the patient was given three doses of sodium iodide, 15 grains (0.97 Gm.), intravenously, but this treatment was discontinued in the absence of any favorable response.

Laboratory Data—The urine was of good concentration throughout the illness, albumin was present in traces, sugar was absent, microscopic examination on various occasions revealed red blood cells, a few white blood cells and occasional hyaline and granular casts. Culture of the urine revealed no organisms. The initial erythrocyte count of 4,640,000, with 80 per cent hemoglobin (Sahli), fell to 3,200,000, with 50 per cent hemoglobin, before death. The leukocyte count gradually rose from 12,000, with 80 per cent polymorphonuclear neutrophils, to a peak of 38,000, with 93 per cent polymorphonuclears. The platelet count was 256,000. The sedimentation rate on November 6 was 41 mm. The Wassermann, Kahn and gonococcus fixation tests gave negative reactions. Agglutination tests for *Bacillus typhosus*, *Bacillus paratyphosus* A and B and *Brucella abortus* gave negative results. Agglutination with *Bacillus proteus* in a dilution of 1:40 was present. Examination of sputum on October 22 revealed no tubercle bacilli. The blood chemistry was normal on admission. On October 29 the icteric index was 17.4, on November 6, the urea nitrogen was 49.2 mg. per hundred cubic centimeters and the icteric index 16.7.

Roentgen examination of the lungs on October 17 gave normal results. On November 6 marked congestion at the bases of both lungs was reported. An electrocardiogram made on October 21 showed only sinus tachycardia. On November 6 the tracings showed sinus tachycardia, inversion of T_1 , low voltage of T_2 and T_3 and left axis deviation.

Each of four cultures of the blood, taken consecutively at intervals over about three weeks, yielded a pure culture of *A. bovis*. Cultures required four to eight days for growth. The organism grew only in the presence of blood and was microaerophilic, requiring reduced oxygen tension for isolation. Morphologically gram-positive, nonacid-fast tangled threads of mycelium were observed, accompanied in older cultures by numerous abnormal forms. This strain was not pathogenic for rabbits (fig 1).



Fig 1—Photomicrograph of a stained specimen of the blood culture

Autopsy—The body was that of a young man of average stature, somewhat emaciated, in complete rigor mortis. The eyes were sunken and the cheeks hollow. There was evident loss of subcutaneous fat. The skin over the face, chest, abdomen and extremities was studded with innumerable petechiae, many of which were white centered. Petechiae were evident also in the conjunctivas. Neither jaundice nor superficial lymphadenopathy was noted.

The panniculus adiposus was thin. The peritoneal surfaces were everywhere smooth and glistening. The small intestine showed occasional bluish-discolored, irregular flecks and contained a small amount of fluid. The liver was enlarged and extended below the costal margin, as did the spleen. The diaphragm was elevated and extended to the level of the fifth interspace on each side.

There were no pleural adhesions. There appeared to be a small amount of blood-tinged fluid in the right side of the chest, although the precise amount could not be ascertained because of the abdominal approach. The lungs were voluminous and heavy. They were crepitant throughout, except for several

circumscribed, bluish segments of atelectasis in the lower lobe posteriorly. The upper lobe of the right lung showed a protruding, circumscribed, firm, nodular lesion, about 1 cm in diameter, with a reddish congested zone around it. On section of this lesion, a cluster of fairly firm, grayish, granular, slightly elevated areas was seen, suggesting small granulomatous nodules or abscesses rather than the ordinary type of bronchopneumonia. Several areas of similar appearance were encountered in the lungs, and sections were taken through these areas. On section, the lungs otherwise had a mottled dark red appearance and exuded frothy fluid on slight pressure. The bronchi also contained pinkish frothy material. There were no enlarged hilar lymph nodes. Microscopic section showed small confluent patches of bronchopneumonia, with exudate of polymorphonuclear leukocytes and apparently some fibrin in alveoli. Several bronchi in the field also contained



Fig 2—Section of the heart, showing vegetation on the mitral valve

purulent exudate, and their walls were infiltrated by polymorphonuclear leukocytes, many brown pigment-containing phagocytes were noted within alveoli. Pulmonary edema was present.

The pericardial surfaces were smooth and glistening. The heart was enlarged and globular, owing to dilatation of both the right and the left ventricle. The myocardium was flabby, soft and pale yellowish brown. The tricuspid, the pulmonary and the aortic valve showed no gross evidences of inflammation. The mitral valve, however, showed a large, soft, friable, yellowish vegetative lesion, involving principally the aortic cusp but distributed also in small clusters along the remainder of the line of closure. The vegetations extended to the anterior and posterior surfaces of the cusps of the valve for some distance, but no destruction or perforation of the valve was noted anywhere (fig 2). The mitral valve showed no evidence of previous valvulitis, no thickening or vascularization of the margin

of the valve was apparent, while the chordae tendineae were slender and delicate and inserted normally in the valve. There was also a small, circumscribed vegetative lesion on the endocardium of the left auricle, similar in appearance to the valvular lesion and situated about 1 cm above it. There was no conspicuous thickening of the auricular endocardium which might suggest an old rheumatic auricular lesion. The papillary muscles and the ventricular endocardium showed nothing noteworthy. Section of the myocardium showed a few small, grayish-discolored areas suggesting embolic lesions, which were taken for section. Microscopic sections showed myocardial degeneration. There were scattered small areas of myocardial necrosis and infiltration with small mononuclear cells and polymorphonuclear leukocytes. Many of these inflammatory foci were perivascular.

The aorta showed scattered yellow intimal atheromatous patches in the descending portion.

The liver was large, soft and yellowish. The anterior surface of both the right and the left lobe showed fibrous perihepatitis and a fibrinous exudate of more recent origin. On section, the lobular outline could be recognized, as well as moderate central lobular congestion, severe parenchymatous degeneration and conspicuous fatty infiltration. The gallbladder and the bile ducts showed nothing abnormal and presented no evidence of infection. The portal vein appeared normal. Microscopic sections showed severe degeneration of liver cells, with vacuolation. The sinusoids were congested and the Kupffer cells enlarged. The periportal fields showed infiltration with mononuclear cells and some eosinophils.

The spleen was markedly enlarged, being approximately 9 to 10 inches (23 to 25 cm) in length and extending about 2 fingerbreadths below the costal margin. It was fairly soft. The surface presented several circumscribed discolored infarcts, varying from 1 to 4 cm in diameter. The pulp on section was dark red and presented prominent grayish nodules and streaks. The splenic artery and vein showed nothing unusual. Microscopic sections showed a number of small infarcts. The malpighian follicles were small. The pulp was hyperemic and contained a considerable number of macrophages and polymorphonuclear leukocytes. Much pigment, most of which was probably due to fixation in solution of formaldehyde was observed, a bacterial clump was seen in an arteriole, the pulp contained many polymorphonuclear leukocytes, including eosinophils and macrophages. Sections also showed an infarct with a congested peripheral zone. No granulomatous or proliferative reaction was noted.

The kidneys were slightly enlarged and were normal in shape and position. The capsule stripped without difficulty, revealing a surface studded with many pinhead-sized reddish petechial lesions, apparently embolic in nature, as well as a number of small yellowish infarcts, about 0.5 cm in diameter. There was rather severe parenchymatous degeneration. The markings of the cortex and medulla were indistinct. The pelvis likewise showed a considerable number of petechial hemorrhages. The ureters appeared normal. The urinary bladder was studded with multiple pinhead-sized petechiae, many of which were white centered. The prostate showed nothing noteworthy. Microscopic sections of the kidneys showed engorgement of interlobular arteries and their branches. The epithelium of the convoluted tubules presented severe degeneration with formation of vacuoles and hyaline droplets. Scattered tubular casts were noted. Focal areas showed interstitial infiltration with polymorphonuclear leukocytes and numerous mononuclear cells. No embolic focal lesions were demonstrated.

The adrenals showed a thin yellow cortex and an autolyzed medulla. Microscopic section showed nothing noteworthy.

The pancreas showed the usual lobular structure. Microscopic sections showed postmortem change.

The stomach showed prominent rugae and moderate congestion. The small intestine, when opened, showed innumerable embolic petechial lesions in the mucosa, many with white centers. Similar lesions were noted in even greater number in the colon, the sigmoid and the rectum. There were no conspicuously enlarged mesenteric lymph nodes.

The brain could not be examined, because the examination was limited. Portions of several lumbar vertebrae were taken for study of the bone marrow.

Bacteriologic Studies—Culture of the crushings of the mitral vegetations revealed *A. bovis*.

Further studies on cultures submitted to the department of bacteriology of the United States Public Health Service confirmed the finding of *A. bovis*.

COMMENT

Ideal criteria for the diagnosis of bacterial endocarditis consist of a number of factors. The clinical picture should conform to the usual accepted standards, positive cultures of a single organism should be obtained from the blood during life, preferably prior to the last week of illness, the same organism should be recovered from the vegetations on the valves. These ideal demands are fulfilled in the case reported. The question whether the condition falls under the acute or the subacute variety need not be of concern here. While it is true that the duration of the illness was only thirty-five days, the case presented the characteristics of the ordinary case of subacute bacterial endocarditis. The use of any time, such as six weeks, as a basis for subdivision is arbitrary and without constant pathologic justification.

The case of Jervell assumes special importance in the present connection, since it is the only case besides mine in which one of the higher bacteria was found as a cause of the endocarditis. The patient was a 20 year old man whose illness began with gastrointestinal symptoms, followed by chills, fluctuating temperature and cutaneous hemorrhages. Embolization of the brain and spinal cord was striking. Death occurred eight weeks after the onset. Autopsy revealed old rheumatic mitral valvulitis, with fresh vegetations on both the aortic and the mitral valve and small ulcerations. The spleen was enlarged and showed many infarcts, some of which were abscessed. Cultures of the blood during life and vegetations of the valves showed *Leptothrix*.

The question of the relation of actinomycosis to cardiac involvement now presents itself. Actinomycosis of the heart is rare. Sanford and Voelker,³ in an exhaustive statistical review of 670 cases of actinomycosis occurring in the United States, failed to find a single case in which the disease involved the heart. Nevertheless, such involvement

³ Sanford, A. H., and Voelker, M. Actinomycosis in the United States. Arch. Surg. 11: 809 (Dec.) 1925.

is not unknown, and cases have been reported by Poncet and Berard,⁴ Benda,⁵ Harbitz and Grondahl,⁶ Letulle and Hufnagel,⁷ Dean⁸ and Kasper and Pinner⁹ In all of these cases, the pericardium and myocardium became involved by direct extension from the pleura and mediastinum or by metastatic spread through the blood stream from a distant focus Dean's case and 1 of those of Harbitz and Grondahl are particularly noteworthy, since endocardial vegetations were seen in addition to the myocardial involvement In both cases the endocardial process was due to direct extension from an underlying myocardial lesion

It is apparent, therefore, not only that endocarditis due to *A. bovis* is a rare complication of actinomycosis but that even when it does occur it is entirely different in its method of invasion and pathogenesis from ordinary bacterial endocarditis Clinically, too, the primary disease dominates the picture

In my case of endocarditis due to *Actinomyces* no portal of entry was demonstrated after a thorough search The clinical picture was indistinguishable from that of ordinary subacute bacterial endocarditis, despite the relatively short duration of its course Pathologically, too, none of the lesions distinctive of actinomycosis was seen The case therefore derives its especial importance from two angles first, the unusual form of involvement of the heart by *Actinomyces* and, second, the unique nature of this etiologic agent as a cause of typical bacterial endocarditis

SUMMARY

A case of bacterial endocarditis due to *A. bovis* is reported Clinically and pathologically it was indistinguishable from an ordinary case of subacute bacterial endocarditis

The Pathological Department of the Hospital for Joint Diseases supplied the pathologic and microbiologic studies in the case and the photographs shown in figures 1 and 2

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4 Poncet, A, and Berard, L. *Traité clinique de l'actinomycose humaine*, Paris, Masson & Cie, 1898

5 Benda, C E. Zwei Fälle von metastasierenden Aktinomykose, *Deutsche med Wchnschr* **26** 70, 1900

6 Harbitz, F, and Grondahl, N B. Die Strahlenpilzkrankheit (Aktinomykose) in Norwegen, *Beitr z path Anat u z allg Path* **50** 193, 1911

7 Letulle, M, and Hufnagel, L. L'actinomycose du coeur, *Bull Acad de med*, Paris **82** 120, 1919

8 Dean, G. A Case of Pyaemic Actinomycosis with an Actinomycotic Endocarditis, *Brit M J* **2** 1303, 1912

9 Kasper, J A, and Pinner, M. Actinomycosis of the Heart. Report of a Case with Actinomycotic Emboli, *Arch Path* **10** 687 (Nov) 1930

PROTAMINE ZINC INSULIN· A METABOLIC STUDY

TREATMENT IN TWO CASES OF SEVERE DIABETES BY EQUALLY
AND UNEQUALLY DIVIDED DIETS WITH COMMENTS
ON CRITERIA FOR TREATMENT

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During the past two years we have treated some of our diabetic patients both in the outpatient department and in the hospital wards with protamine zinc insulin. Like others² we hoped that by virtue of its slow activity a single daily dose of this new preparation could be substituted for three or even four doses of regular insulin. However, when we put this thought into practice we experienced considerable difficulty in maintaining the urine free from sugar. We appreciated the facts that we employed the higher carbohydrate diet—200 to 250 Gm.—and that we had not worked out a technic for the use of protamine insulin. As a matter of fact there is no definitely established technic for the administration of this preparation. All sorts of combinations² are recommended with or without the addition of regular insulin—that is two or more hypodermic injections daily. It was and still is our feeling that if advantage is to be taken of the slow-acting property of protamine insulin efforts should be directed to treatment of the diabetic patient by means of *one* dose daily. Such a procedure would relieve the patient

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1 Adlersberg D. *Wien klin Wchnschr.* 49:476 1936. Kerr R. B. and Best C. H. *Canad. M. A. J.* 34:400 1936. Krarup N. B. *Clinical Investigations into the Action of Protamine Insulinate*, translated by C. L. Heel, Copenhagen G. E. C. Gad Publisher 1935. Lawrence K. D. and Archer N. *Brit. M. J.* 1:747 1936. Rabinovitch I. M., Fowler A. F. and Corcoran, A. C.: *Canad. M. A. J.* 35:239 1936. Root H. F., White, P., Marble, A. and Stotz, E. *Clinical Experience with Protamine Insulinate*, *J. A. M. A.* 106:189 (Jan 18) 1936. Sprague, R. G., Blum B. B., Osterberg A. E.; Keppler E. J. and Wilder, R. M. *Clinical Observations with Insulin Protamine Compound*, *ibid.* 106:1701 (May 16) 1936. Keppler E. J. *Clinical Experience with Protamine Zinc Insulin*, *J. A. M. A.* 110:92 (Jan 8) 1938.

2 Tolstoi E. *Am. J. M. Sc.* 194:727, 1937.

of the burdensome routine of carrying his medication about and eating his meals at definite intervals in relation to the administration of insulin. And, as Mosenthal³ aptly stated

The resort to protamine zinc insulin should do away with these restrictions, the ideal to be attained is that one dose of protamine zinc insulin is given in the morning before breakfast when the routine preparations for the day are carried out, and the meals are taken at optional hours with no anxiety about their being served exactly on time. Any deviation from this schedule does not fulfil the complete purpose of protamine zinc insulin.

To attain this ideal with a liberal carbohydrate diet, various dietary divisions instead of the customary three equal portions of carbohydrate throughout the day have been recommended. The Danish discoverers⁴ of protamine insulin were the first to suggest the irregular distribution of the carbohydrate fraction. S. Harris and S. Harris Jr.⁵ recommended six meals in place of the usual three. Other investigators⁶ advised that the day be started with a small carbohydrate meal and that some carbohydrate be given before bedtime. Another method was to fractionate the total carbohydrate into $\frac{1}{5}$, $\frac{2}{5}$, $\frac{2}{5}$ for three meals and then subtract 10 to 15 Gm. of carbohydrate from each meal, to be given two to three hours after each meal. Pollack and Lande⁷ have experimented with such dietary divisions, and they have no one fixed formula as yet. They used the method which gave them the best results, and in some cases it was a $\frac{1}{5}$, $\frac{2}{5}$, $\frac{2}{5}$ division of the carbohydrate, in others it was $\frac{1}{5}$, $\frac{1}{5}$, $\frac{3}{5}$, or $\frac{2}{5}$, $\frac{1}{5}$, $\frac{2}{5}$. They further advised the omission at breakfast of foods containing immediately available sugar, such as fruit juices.

A perusal of the literature reveals that some or all of these methods are in use. It is also apparent that both the low and the high carbohydrate diet are employed. And, as there are no detailed data on record which deal with the response of the *same* diabetic patient to these various fractional dietary divisions or to a high or a low carbohydrate diet while one dose of protamine insulin is being received daily, we felt that a study of this type would be of interest. We set before

3 Mosenthal, H. O. Protamine Zinc Insulin. Clinical Application, J. A. M. A. **110** 87 (Jan. 8) 1938.

4 Hagedorn, H. C., Norman Jensen, B., Krarup, N. B., and Wodstrup, I. Protamine Insulinate, J. A. M. A. **106** 177 (Jan. 18) 1936.

5 Harris, S., and Harris, S., Jr. Am. J. Digest. Dis. **5** 88, 1938.

6 Protamine Insulin and Diet in Diabetes Mellitus, editorial, Ann. Int. Med. **11** 2048, 1938.

7 Pollack, H., and Lande, H. New York State J. Med. **38** 339, 1938.
Pollack, H. J. Mt. Sinai Hosp. **4** 437, 1938.

us the following three questions, the answers to which we hope may be of considerable help in the treatment of the diabetic patient

1 Is glycosuria affected materially by shifting the diet from $\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$ to $\frac{1}{5}$, $\frac{2}{5}$, $\frac{2}{5}$ if all other factors remain constant?

2 Is the patient's diabetes better managed with a lower than with a higher carbohydrate diet?

3 What are to be considered criteria for the "control" of diabetes?

PLAN OF EXPERIMENT

The subjects of our study were 2 "healthy" female diabetic women. Their diabetes was severe, as can be noted from their respective clinical histories, which will be given. During the eighteen months prior to the writing of this report neither was free from glycosuria, even though each received 50 to 80 units of insulin—protamine as well as regular. Prior to admission they adhered to their diets as well as they could. They are intelligent persons, and they made every effort to cooperate.

We hospitalized both patients, one for fifty and the other for sixty days. Both were under rigid supervision in the metabolism ward. Each was given a diet of 75 Gm of protein, 60 Gm of fat and 200 Gm of carbohydrate, a total of 1,640 calories. As the protocols show, 1 of the patients was given 50 and the other 60 units of protamine zinc insulin daily before breakfast. The experiment was divided into ten day periods. During the first, the diet was fractioned into three approximately equal portions. During the second period the distribution of the diet was $\frac{1}{3}$, $\frac{2}{3}$, $\frac{2}{3}$. We then resumed the original proportions of $\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$ for another ten days. At the end of these three periods the carbohydrate fraction was reduced by one-half, and to maintain the diet isocaloric the same number of calories was added to the fat. The new diet consisted of 75 Gm of protein, 105 Gm of fat and 100 Gm of carbohydrate. The daily dose of insulin remained the same throughout the entire experiment, as did the quantity of protein. The figure of 100 for carbohydrate was not selected at random. We observed that our patients excreted about 100 Gm of dextrose a day. This excretion was, of course, variable, but the total output for the first thirty days was 3,000 Gm. Since the patients failed to utilize this amount, we felt that a deduction of the daily average excretion—100 Gm—from the original diet was reasonable. After the patients were given the lower carbohydrate diet, they again were observed when the division of the food was $\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$, when it was $\frac{1}{5}$, $\frac{2}{5}$, $\frac{2}{5}$ and when it was $\frac{2}{5}$, $\frac{1}{5}$, $\frac{2}{5}$. The patients were not in bed all the time. They were seen daily and questioned as to symptoms of diabetes and as to their well-being in general. Their weight was recorded daily.

Every specimen of urine voided was preserved in a separate receptacle. Each one was tested for dextrose qualitatively. The specimens for a twenty-four hour period were then pooled, and, after the daily volume was noted, the total amount of dextrose as well as of nitrogen was determined. Tests for acetone also were done daily on the total twenty-four hour specimen.

On the eighth day of *each* period a blood sugar curve was recorded. This was taken during fasting and at 11 a. m., and 1, 4 and 7 p. m.

The Benedict qualitative and quantitative method was used for the determination of the urinary sugar. Acetone was determined by the Rothera test. The

Folin-Wu method was used for the analyses of blood sugar and the Bloor method for the estimation of cholesterol

REPORT OF CASES

CASE 1—F H, a 27 year old single white woman, whose personal history and family history revealed no facts contributory to the present situation, about four years before noted continued hunger, thirst and marked loss of weight, in spite of eating a good deal and drinking large amounts of water. At that time she had to be fitted for glasses because of blurred vision. The menstrual periods became scantier during the three to four months these symptoms were present, and her weight dropped from 140 pounds (63.5 Kg) to 114 pounds (52 Kg). While treating her for a minor injury, a chiropractor elicited the aforementioned symptoms and on examining a specimen of her urine told her that she had diabetes and sent her to the clinic at Billings hospital in Chicago, in July 1934. Physical examination at that time revealed no abnormalities other than that the liver was felt at 2 cm below the costal margin. Glycosuria (4 plus) was present, and the urine gave a 2 plus reaction for acetone. She was given a diet of 60 Gm of protein, 175 Gm of fat and 100 Gm of carbohydrate, and after some treatment she was finally discharged on the same diet with insulin in doses of 16-6-12. On this regimen her weight rose to 130 pounds (59 Kg) in January 1935. However she continued to have either insulin reactions or glycosuria. In January 1937, while in Florida, she contracted a cold, which was diagnosed as influenza. She was ill for about a month. Her weight dropped to 111 pounds (50.5 Kg), and of course the glycosuria could not be regulated at that time.

On her return from Florida she came to the diabetic clinic of the New York Hospital, in May. On her admission the diet consisted of 60 Gm of protein, 175 Gm of fat and 100 Gm of carbohydrate, with insulin in doses of 30-15-15. Glycosuria (4 plus) was present and the urine gave a 3 plus reaction for acetone. The results of the physical examination were in no way contributory. The diet was changed at this time to 70 Gm of protein, 60 Gm of fat and 200 Gm of carbohydrate, with the dose of insulin as stated, 30-15-15. At almost every visit to the clinic she had glycosuria (4 plus) and a 0 to 2 plus reaction for acetone in the urine. She stated that the insulin reactions were troublesome. Since she seemed to be the type in which the blood sugar oscillates, it was decided to try protamine insulin, and in July she was given 40 units of protamine and 15 units of regular insulin before breakfast. On this regimen she felt better than she ever did before. Her weight rose to 134 pounds (60 Kg), but she continued to have irregular glycosuria. As she continued to have occasional reactions, the dose was reduced to 35 units of protamine and 10 units of regular insulin in the morning. From August to February 1938 she felt well and took care of herself. She was excreting sugar all the time during her absence. She reported to the hospital in February because of this constant glycosuria and an infection of the gum. In view of the fact that she had severe diabetes which was difficult to regulate, she was requested to enter the metabolism ward for study.

On her admission the physical examination revealed nothing abnormal except for a slight infection of the gum, which was treated. The urine revealed sugar (4 plus) but no albumin or red blood cells. The erythrocyte count was 4,900,000, with 94 per cent hemoglobin, and the leukocyte count 8,200, with a normal differential count. The blood sugar content during fasting was 214 mg per hundred cubic centimeters. The blood showed no serologic abnormality, and the basal metabolic rate was ± 7 per cent.

CASE 2—M D, an 18 year old white girl, who has been followed closely for the past six years, was first seen in April 1932, at the age of 12 years, during a bout of diabetic ketosis necessitating admission to the hospital. A paternal grandfather died of diabetes at 65. The child grew and developed normally. About March 1932 she lost 12 pounds (5.4 Kg) in two weeks' time, she was hungry and voided large amounts of urine. She became irritable and lethargic about six days before admission. She began to have epigastric pain and vomiting, and since the abdominal pain persisted she was brought to the clinic. At that time there was a marked odor of acetone on her breath. She felt dry and was sleepy. The urine had a 4 plus reaction for sugar and a 4 plus reaction for acetone. The sugar content of the blood was 625 mg per hundred cubic centimeters. She was admitted to the hospital, where she responded satisfactorily to treatment and was discharged on a diet of 85 Gm of protein, 110 Gm of fat and 120 Gm of carbohydrate, with insulin in doses of 10-0-10.

After her first admission she was in the hospital ten times. At no time after the discovery of her diabetes had her urine been sugar free, either at the hospital or at home. All sorts of dietary combinations as well as doses of insulin have been tried, but at no time was there continuous freedom from glycosuria. Whenever the dose of insulin was increased she was brought to the hospital because of profound shock. In spite of this difficulty, she continued to develop and grow. Her menses became established in 1935. In April of that year she was admitted to the hospital because of otitis media and acute mastoiditis, due to the beta hemolytic streptococcus. Mastoidectomy was done, and she made a good recovery, after which she was discharged on a diet of 70 Gm of protein, 50 Gm of fat and 250 Gm of carbohydrate, with insulin in doses of 40-20-20. She continued to excrete sugar on this regimen, and the dose of insulin was changed to 30-20-20-10. Because some reactions occurred on this regimen the dose was reduced to 20-15-15-5. She began to gain weight and "felt fine," but the diet and the dose of insulin had to be altered constantly because of difficulty in adjustment. During this time her menses were irregular, and an estrogemic preparation (amniotin) was given, 2,000 to 10,000 units every other day for a month, but without success.

In June 1938 protamine insulin was administered in the evening, with regular insulin in the morning and at noon, and though the patient felt well she continued to excrete sugar. Thus she was treated, as has been described, by means of every conceivable combination of diet and insulin, but at no time could one obtain the laboratory ideal of satisfactory therapy. In view of the fact that she continued to develop normally, gain weight and height, and carry on in a perfectly normal manner in school, leading her class, in spite of constant glycosuria, less and less attention was being paid to that condition.

When she was admitted to the hospital, about April 1938, because of a slight infection of the upper part of the respiratory tract, it was decided to place her in the metabolism ward for study. A diet of 75 Gm of protein, 60 Gm of fat and 200 Gm of carbohydrate was prescribed and one dose of protamine insulin given daily. The laboratory data other than those concerned with the diabetes were of no importance.

ANALYSIS OF DATA

At the outset we wish to emphasize that during the entire period of observation both patients felt perfectly well. Neither revealed a single symptom of diabetes. As can be seen in the tabulated data, F H lost

TABLE 1—Data for Patient F H

Date	Weight, Kg	Diet per 24 Hr				Protein, Gm	Fat, Gm	Carbohy- drate, Gm	Calories	Division of Diet	Protamine Insulin, Units (10 regular insulin)	Amount	Urine per 24 Hr			
		Protein, Gm	Fat, Gm	Carbohy- drate, Gm	Calories								Sugar, Gm	Sugar, %	Total Nitro- gen, Gm	Nitrogen Balance*
2/23/38	60.6	49	41	124	1,095	1/3, 1/3, 1/3				1/3, 1/3, 1/3	40	2,365	104	4.4	9.18	+1.63
3/1/38	59.73	75	60	199	1,687	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	2,420	156.5	6.5	10.5	+0.3
3/2/38	59.6	75	59	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	2,210	125	5.6	10.75	+0.05
3/3/38	59.7	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	2,510	191	7.6	11.3	-0.5
3/4/38	59.68	75	60	199	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	2,275	193	8.5	10.71	+0.99
3/5/38	59.6	75	59	199	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,985	172	7.7	10.9	-0.1
3/6/38	59.2	75	60	199	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,540	96	6.2	10.75	+0.05
3/7/38	59.38	75	59.8	199	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	2,015	132	6.5	11.25	-0.45
3/8/38	59.19	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,195	90.9	6	11.3	-0.5
3/9/38	59.46	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	2,410	144	5.9	12.9	-2.1
3/10/38	58.85	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,440	134	10.7	10.55	+0.25
3/11/38	58.92	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	50	1,090	41.8	3.8	9.7	+1.1
3/12/38	58.94	75	60	200	1,640	1/5, 2/5, 2/5				1/5, 2/5, 2/5	50	1,495	39	4.2	9.7	+1.1
3/13/38	58.92	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	50	1,505	143	9	10.3	+0.5
3/14/38	58.59	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	70	1,715	143	8.2	11.14	-0.84
3/15/38	58.46	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	50	930	11	4.4	9.82	+1.48
3/16/38	58.82	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	70	1,040	31.3	3	9.35	+1.45
3/17/38	58.84	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	70	1,515	111	7.3	9.65	+1.15
3/18/38	58.82	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	70	1,265	51.8	1.1	9.7	+1.1
3/19/38	58.96	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	50	1,420	70.8	2.2	9.35	+1.45
3/20/38	58.67	75	60	200	1,640	1/5, 2/5, 2/5				1/5, 2/5, 2/5	50	1,285	41.5	3.5	9.03	+1.77
3/21/38	58.87	75	60	200	1,640	1/3, 2/5, 2/5				1/3, 2/5, 2/5	50	1,570	63.3	4.1	9.64	+1.16
3/22/38	58.4	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,700	125	8.5	10.3	+0.5
3/23/38	58.73	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	975	30.8	3.1	8.63	+2.17
3/24/38	59.25	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	1,620	81.5	5.1	9.82	+0.88
3/25/38	58.91	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,115	14.3	1.2	9.23	+1.55
3/26/38	58.89	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,440	61.5	4.2	9.93	+0.87
3/27/38	58.85	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,730	143	8.2	11.6	-0.8
3/28/38	58.89	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,040	83.5	8	9.36	+1.44
3/29/38	58.84	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	1,260	80	6.6	9.92	+0.88
3/30/38	58.51	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,505	100	6.5	10.63	+0.17
3/31/38	58.46	75	60	200	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,650	87	5.3	10.08	+0.72
4/1/38	58.48	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	865	26	0.3	9.37	+1.40
4/2/38	59	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,115	9.15	0.7	9.92	+0.88
4/3/38	58.82	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	1,170	8.35	0.7	6.22	+4.58
4/4/38	58.82	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,010	0	0	10.74	+0.06
4/5/38	58.92	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,210	14.3	1.2	10.52	+0.28
4/6/38	58.43	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	1,255	5.5	0.4	10.49	+0.1
4/7/38	58.42	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	925	0	0	9.53	+1.21
4/8/38	58.5	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,280	23.6	1.8	10.4	+0.4
4/9/38	58.32	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,105	10	3.6	10.02	+0.78
4/10/38	57.96	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	70	945	0	0	9.63	+1.17
4/11/38	58.22	75	105	100	1,640	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	945	0	0	9.75	+1.05
4/12/38	58.24	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	1,040	0	0	8.75	+2.05
4/13/38	58.19	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	1,255	37.2	2.9	11.92	-1.12
4/14/38	57.76	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	975	6.25	0.6	10.08	+0.72
4/15/38	58.31	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	860	0	0	9.92	+0.88
4/16/38	58.04	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	890	3.61	0.4	9.03	+1.77
4/17/38	57.87	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	850	0	0	10.63	+0.17
4/18/38	58.48	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	70	1,515	0	0	10.35	+0.45
4/19/38	58.44	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	70	1,475	16.4	1.1	9.58	+1.22
4/20/38	57.93	75	105	100	1,640	2/5, 1/5, 2/5				2/5, 1/5, 2/5	50	850	5	0.6	9.14	+1.66
4/21/38	58.07	75	115	125	1,895	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	1,185	18.9	1.6	10.3	+0.5
4/22/38	58.37	75	115	125	1,895	1/3, 1/3, 1/3				1/3, 1/3, 1/3	50	915	12.5	1.3	9.65	+1.15

* Ten per cent of the nitrogen of the food is calculated as being excreted in the feces

TABLE 2—Data for Patient M D

Date	Weight, Kg	Diet per 24 Hr				Protamine Insulin, Units	Urine per 24 Hr				Nitrogen Balance*
		Protein, Gm	Fat, Gm	Carbohy- drate, Gm	Calories		Amount	Sugar, Gm	Sug u, %	Total Nitro- gen, Gm	
4/24/38	50.36	75	60	200	1,640	60	3,715	301.5	8.1	11.6	-0.8
4/25/38	49.18	75	60	200	1,640	60	2,480	136.2	6.3	10.35	+0.17
4/26/38	48.28	75	60	200	1,640	60	1,725	88.5	4.8	8.37	+2.23
4/27/38	48.92	75	60	200	1,640	60	1,620	80	1.9	9.21	+1.53
4/28/38	49.20	75	60	200	1,640	60	1,925	21.8	2.3	6.97	+3.87
4/29/38	49.37	75	60	200	1,640	60	1,485	66.8	1.3	8.68	+2.12
4/30/38	49.43	75	60	200	1,640	60	1,480	58.8	3.9	8.71	+2.07
5/1/38	49.3	75	60	200	1,640	60	1,860	71.5	5.2	9.13	+1.67
5/2/38	49.25	75	60	200	1,640	60	1,455	83.5	5.7	8.38	+2.22
5/3/38	49.28	75	60	200	1,640	60	1,120	11.8	3.7	7.23	+3.57
5/4/38	49.33	75	60	200	1,640	60	1,915	149.5	7.1	9.29	+1.31
5/5/38	49.12	75	60	200	1,640	60	2,170	129	5.9	12.97	-2.15
5/6/38	49.63	75	60	200	1,640	60	1,845	64.5	4.8	9.92	+0.88
5/7/38	49.8	75	60	200	1,640	60	1,755	87	5.6	8.88	+2.22
5/8/38	49.8	75	60	200	1,640	60	1,925	110	5.7	10.65	+0.15
5/9/38	49.55	75	60	200	1,640	60	1,400	71.2	5.3	11.01	-0.21
5/10/38	49.65	75	60	200	1,640	60	2,025	107	5.3	10.85	-0.07
5/11/38	49.63	75	60	200	1,640	60	2,170	143.8	6.6	10.12	+0.68
5/12/38	49.65	75	60	200	1,640	60	1,675	111	6.6	8.63	+2.27
5/13/38	49.61	75	60	200	1,640	60	1,875	93.5	5	8.97	+1.83
5/14/38	49.59	75	60	200	1,640	60	1,940	95.3	1.9	9.92	+0.88
5/15/38	49.23	75	60	200	1,640	60	1,970	100	5.1	11.38	-0.58
5/16/38	49.14	75	60	200	1,640	60	1,675	87	5.2	11.1	-0.3
5/17/38	49.5	75	60	200	1,640	60	2,220	115	5.1	11.15	-3.35
5/18/38	49.65	75	60	200	1,640	60	1,625	93.5	5.7	11.2	-0.1
5/19/38	49.92	75	60	200	1,640	60	1,505	71	1.9	10.8	-0.1
5/20/38	49.86	75	60	200	1,640	60	2,655	136	5.1	12.63	-1.83
5/21/38	50.07	75	60	200	1,640	60	2,215	139	6.2	10.14	+0.66
5/22/38	49.83	75	60	200	1,640	60	1,630	67	6.5	6.93	+3.87
5/23/38	49.3	75	60	200	1,640	60	1,415	83.5	5.9	10.38	+0.42
5/24/38	49.61	75	105	100	1,640	60	940	28.6	3	9.35	+1.15
5/25/38	49.85	75	105	100	1,640	60	1,220	50	1.1	9.08	+1.72
5/26/38	49.33	75	105	100	1,640	60	1,775	87	1.9	12.1	-1.3
5/27/38	49.33	75	105	100	1,640	60	845	40	4.7	7.45	+3.35
5/28/38	49.66	75	105	100	1,640	60	1,280	69	5.1	9.12	+1.38
5/29/38	49.91	75	105	100	1,640	60	1,370	66.8	1.9	9.08	+0.82
5/30/38	49.5	75	105	100	1,640	60	1,650	83.3	5	11.2	-0.10
5/31/38	49.92	75	105	100	1,640	60	1,500	69	1.6	11.2	-0.10
6/1/38	48.61	75	105	100	1,640	60	1,035	19.7	1.9	9.98	+0.82
6/2/38	48.7	75	105	100	1,640	60	1,640	83.3	5.1	11.3	-0.3
6/3/38	48.48	75	105	100	1,640	60	2,045	91.7	1.1	9.42	+1.38
6/4/38	48.63	75	105	100	1,640	60	1,785	95.5	6	9.88	+0.92
6/5/38	49.25	75	105	100	1,640	60	1,205	71.2	6.1	8.58	+2.22
6/6/38	49.55	75	105	100	1,640	60	1,255	76	6.1	8.85	+1.95
6/7/38	49.68	75	105	100	1,640	60	1,615	91	5.6	11.35	-0.55
6/8/38	49.6	75	105	100	1,640	60	1,995	116.8	5.8	13.03	-2.23
6/9/38	49.19	75	105	100	1,640	60	1,130	78.2	5.1	10.16	+0.1
6/10/38	49.97	75	105	100	1,640	60	830	15.5	5.1	6.72	+1.08
6/11/38	49.68	75	105	100	1,640	60	2,075	115	5.5	11.1	-0.3
6/12/38	49.35	75	105	100	1,640	60	1,900	113.5	6.0	15.1	-1.3
6/13/38	49.23	75	105	200	1,640	60	2,235	140.5	6.3	12.1	-1.6
6/20/38	48.97	75	60	200	1,640	60	1,990	117.5	5.9	10.87	-0.07
6/21/38	49.66	75	60	200	1,640	60	2,255	151	6.7	11.05	-0.25
6/22/38	49.19	75	60	200	1,640	60	1,870	97.3	5.2	10.1	+0.4
6/23/38	49.68	75	60	200	1,640	60	1,915	105	5.1	9.34	+1.16
6/24/38	49.2	75	60	200	1,640	60	2,015	137.5	6.8	10.5	+0.3
6/25/38	49.19	75	60	200	1,640	60	1,640	95.5	5.8	9.32	+1.23
6/26/38	49.15	75	60	200	1,640	60	2,175	116	1.7	10.82	-0.02
6/27/38	48.63	75	60	200	1,640	60	2,015	98.5	1.7	10	+0.8
6/28/38	48.21	75	60	200	1,640	60	1,755	89.3	3	10.55	+0.25

* Ten per cent of the nitrogen of the food is calculated as being excreted in the feces

1.34 Kg in fifty days and M. D. 0.97 Kg in sixty days. The former received 28 calories per kilogram, while the latter received 33.5 calories per kilogram. Both patients were on subcaloric diets as judged by the Aub-Du Bois⁸ standards.

Neither patient had nocturia. F. H. had her menstrual period at the expected time, M. D. had a period for the first time in months while living on this regimen.

Urine—F. H. showed sugar in the urine except for seven times, and *most fractional specimens gave a 4 plus reaction*. M. D.'s urine was never sugar free during her entire stay in the hospital and all fractional specimens revealed glycosuria (4 plus), *no ketone bodies were present*. The volume of urine ranged between 850 and 2,500 cc except on one occasion when M. D. had severe glycosuria with a volume of 3,700 cc for the twenty-four hour period. The excretion of sugar was totally irregular, and, even though every attempt was made to keep the conditions of the experiment constant, it was impossible to predict whether the total dextrose excreted would be high or low. When the total excreted dextrose was subtracted from the total intake (exclusive of the dextrose derived from the protein and fat) the amounts utilized were not markedly different whether the diet was divided into $\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$ or $\frac{1}{5}$, $\frac{2}{5}$, $\frac{2}{5}$ or any combination indicated in the tables. During the first thirty days, while receiving 200 Gm of carbohydrate daily, or a total of 6,000 Gm, each patient excreted a total of about 3,000 Gm of sugar—an average of 100 Gm per day. When the carbohydrate intake was reduced to 100 Gm a day the excretion of dextrose fell definitely, but even on this regimen the division of the diet into $\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$ or $\frac{1}{5}$, $\frac{2}{5}$, $\frac{2}{5}$ made little difference, except that the glycosuria was heavier when the diet was unevenly partitioned. Actually, F. H. excreted 128 Gm of dextrose in twenty days with a 2,000 Gm intake, and M. D. excreted 1,443 Gm with a 2,000 Gm intake.

The nitrogen balance of both patients was positive during the experimental period, though there were occasional days when they excreted more nitrogen than they ingested.

Blood Sugar Curve—A review of the data in table 3 shows that though the sugar content of the specimens of the blood taken during fasting was variable, nevertheless it was within or close to normal limits. It is clear also that the dextrose content of all the postprandial specimens was considerably elevated and that this hyperglycemia was sustained irrespective of the type of diet used or the manner in which

8 Aub, J. C., and Du Bois, E. F. Clinical Calorimetry. XIX. The Basal Metabolism of Old Men, Arch. Int. Med. 19: 823 (May) 1917.

it was fractionated. In the case of F H the blood sugar curves were lower after the first ten day period, but, as can be seen neither the type nor the division of the diet influenced them materially. This was true in general in the case of M D, also with perhaps a more pronounced elevation when she was receiving the higher carbohydrate diet. The division of the diet into unequal portions failed to affect either the character or the absolute values significantly.

In the record of M D (table 2) there is an interruption of the daily sequence from June 13 to June 20, 1938. During this period, because of a misunderstanding, she consumed a package of diabetic ginger snaps. These had little carbohydrate value but were rich in protein and fat. All the data collected during this period were therefore discarded.

This unpleasant incident caused a thorough investigation as to the reliability of data on the dietary intake. F H had no visitors during

TABLE 3—*Blood Sugar Content for Patients F H and M D*

Date	Patient F H					Diet (Gm)	Dietary Divisions
	8 a m Fasting	11 a m	1 p m	4 p m	7 p m		
3/ 7/38	192	272	333	288	323	Protein 75, fat 60, carbohydrate 200	1/3, 1/3, 1/3
3/18/38	95	180	166	205	250	Protein 75, fat 60, carbohydrate 200	1/5, 2/5, 2/5
3/31/38	64	241	226	194	220	Protein 75, fat 60, carbohydrate 200	1/3, 1/3, 1/3
4/ 8/38	55	192	214	211	276	Protein 75, fat 105, carbohydrate 100	1/3, 1/3, 1/3
4/19/38	100	185	211	220	241	Protein 75, fat 105, carbohydrate 100	2/5, 1/5, 2/5
Patient M D							
5/ 2/38	150	454	428	375	375	Protein 75, fat 60, carbohydrate 200	1/3, 1/3, 1/3
5/11/38	79	365	444	357	468	Protein 75, fat 60, carbohydrate 200	1/5, 2/5, 2/5
5/21/38	172	333	340	319	375	Protein 75, fat 60, carbohydrate 200	1/3, 1/3, 1/3
5/31/38	133	306	326	365	333	Protein 75, fat 105, carbohydrate 100	1/3, 1/3, 1/3
6/10/38	68	214	272	267	340	Protein 75, fat 105, carbohydrate 100	1/5, 2/5, 2/5

* The values for the blood sugar are expressed in milligrams per hundred cubic centimeters

her stay in the hospital and she stated most emphatically that she committed no dietary mistakes or indiscretions.

M D insisted that apart from eating the diabetic ginger snaps she adhered to the diet most carefully, and, after she was told that the results obtained during the dietary break would have to be discarded, she exercised most meticulous care during the last ten day period. We, therefore, are reasonably confident that no dietary breaks, other than the one mentioned, occurred. We feel that this explanation is essential, as our results are so striking as to suggest that additional food might have been ingested. To the best of our knowledge and that of our dietetic staff such was not the case with the one exception already mentioned.

COMMENT

The treatment of diabetes mellitus has been constantly changing, chiefly because of the introduction of insulin and later of protamine insulin. The attitude toward the blood sugar levels and the sugar-

free urine has changed. It may still be desirable to balance the diet with insulin so as to maintain the urine free from sugar, but today glycosuria and consequently persistent or intermittent hyperglycemia may be acceptable as adequate regulation. Then, too, the diet has been changing. There are the high carbohydrate and the low carbohydrate diet, there is the "free diet," or no diet at all, of Stolte,⁹ and since the introduction of protamine insulin there has been discussion of the merits and advantages of equal and unequal divisions of the diet. Among our ambulatory patients receiving protamine zinc insulin we have observed constant and persistent glycosuria for about one and one half years. They were in excellent condition. No attempt was ever made to quantitate this sugar, as we would not have been certain as to the reliability of collection. The patients whose cases have been presented also excreted large amounts of sugar daily. This phenomenon was more marked with a high than with a low carbohydrate diet. They felt perfectly well, were symptom free and did not excrete ketone bodies in the urine. Furthermore, dividing their diets into equal or unequal portions influenced the quantitative excretion of dextrose little. The blood sugar curves were also affected little by such dietary division. True, decreasing the carbohydrate fraction caused a marked fall in the urinary dextrose, but at the same time the utilization was considerably decreased. The point that we wish to emphasize is that with the use of protamine insulin even severe glycosuria is compatible with good health, maintenance of weight and nitrogen equilibrium, as well as freedom from the symptoms of diabetes and ketosis. A similar status was observed by Raiha,¹⁰ who studied diabetic children. With two doses of regular insulin daily at times as high as 40 units at each injection, his patients felt well, grew, developed, resisted infection and did not excrete ketone bodies, in spite of constant and marked glycosuria and a blood sugar content during fasting of 500 mg per hundred cubic centimeters.

It is now accepted that with the employment of protamine insulin glycosuria is permissible. Qualitatively a 4 plus reaction is allowed, quantitatively no definite limit has been established. In this connection it is significant to present the view of Joslin¹¹ and his associates.¹² Until recently they had always insisted on sugar-free urine. Now this group have warned the physician not to expect perfection when using protamine insulin. They have expressed more liberal views than ever before and stated that they are not discouraged if heavy glycosuria is

9 Stolte, K. *Med Klin* **27** 831, 1931

10 Raiha, C. E. *Acta pædiat* **19** 433, 1937

11 Joslin, E. P. *Mil Surgeon* **82** 1, 1938

12 White, P. *South M J* **31** 15, 1938

found in the fractional specimens. They pay much more attention to the total twenty-four hour excretion. Their "standard of control, based upon the twenty-four hour quantitative specimen of urine, is no longer 100 but 90 per cent." In other words, they expressed the feeling that if a patient is receiving 150 Gm of carbohydrate and his total excretion in twenty-four hours is 15 Gm the condition is adequately controlled. There are others⁶ who ignore as much as 40 Gm of dextrose in a twenty-four hour specimen of urine. Our patients, during the periods studied, often excreted much more than 100 Gm daily, and they showed no ill effects either subjectively or objectively. Obviously, at present there can be no set rule as to the quantity of dextrose one is or is not permitted to excrete if the condition is to be considered well regulated. All this leads, of course, to further speculation. Whether a patient excretes 15 Gm of sugar or more during a twenty-four hour period, he is sure to have either continuous or intermittent hyperglycemia. That is inevitable. The question therefore arises whether hyperglycemia is deleterious. As yet there is no definite reply. It has been repeatedly stated that hyperglycemia renders a diabetic patient more susceptible to infections. It has been maintained also that hyperglycemia is an etiologic factor in the atherosclerosis of the diabetic patient. Neither of these postulates has been convincingly established, and formidable objections can be raised against most hypotheses. It is important to call attention to the fact that such theories were formulated during the preinsulin era. And no doubt during that period patients with the more severe forms of diabetes were in a deplorable state of nutrition, they were desiccated and debilitated, all of which may have been conducive to increased susceptibility to infections and degenerative lesions. Today, the diabetic patient is well nourished, whether or not he reveals glycosuria and hyperglycemia. Insulin—regular and protamine—has changed the status of the diabetic patient. With improved nutrition, even in the presence of glycosuria many of our ambulatory insulin-treated patients suffered from no more frequent or more severe infections than nondiabetic persons. Considerable doubt has been cast on the effect of hyperglycemia on infections, by Mosenthal,¹³ Bayne-Jones¹⁴ and Richardson¹⁵. Also Marble, White and Fernwald¹⁶ expressed the feeling that present day diabetic patients are not more susceptible to infections than normal persons. From most carefully planned and excellently presented experiments they con-

13 Mosenthal, H. O. Hyperglycemia. Evaluation in the Treatment of Diabetes Mellitus, *J. A. M. A.* **105** 484 (Aug. 17) 1935.

14 Bayne-Jones, S. *Bull. New York Acad. Med.* **12** 278, 1936.

15 Richardson, R. *J. Clin. Investigation* **12** 1143, 1933, **14** 389, 1935.

16 Marble, A., White, H. J., and Fernwald, A. J. *J. Clin. Investigation* **17** 423, 1938.

cluded that " whole blood of diabetic patients were found to possess essentially the same phagocytic, bacteriostatic and bactericidal power against selected strains of streptococci as blood from normal controls "

Evidence that hyperglycemia and glycosuria are the etiologic factors in the vascular sclerosis is not convincing The projected hypotheses have been multiple, conflicting and confusing The clinical observations of many investigators have not yielded uniform results One of us (E T) and an associate ¹⁷ have observed roentgen evidence of calcium deposits in the tibial vessels in a young diabetic patient whose diabetes was only two months old, and we have failed to find this vascular change in patients with severe diabetes of from five to twelve years' duration who revealed glycosuria most of the time These patients were receiving insulin and were well nourished Experimentally, MacLeod ¹⁸ could not demonstrate vascular lesions in depancreatized dogs which were maintained in a good state of nutrition by means of insulin but revealed hyperglycemia and glycosuria for over four years Such data convince us that the same hypotheses are not applicable to diabetic patients treated with and to those treated without insulin We believe that the administration of insulin, no matter how unsatisfactorily we imitate the biologic mechanism, offers *protection* to the diabetic patient

The use of insulin has been instrumental in somewhat modifying the point of view concerning the deleterious effects of hyperglycemia and glycosuria, and, furthermore, since the introduction of protamine insulin even the most conservative investigators permit glycosuria, it is therefore obvious that our criteria for so-called adequate control must be revised Stolte ⁹ and Raiha ¹⁰ have been guided chiefly by the clinical response and have paid no attention to glycosuria or hyperglycemia However, they have insisted on acetone-free urine In this country the excretion of 15 to 40 Gm of dextrose by patients treated with protamine insulin has been accepted as adequate control For cases managed in our outpatient department we have no quantitative data But in the cases here presented we have observed glycosuria with a sugar content of 100 Gm per twenty-four hours and more We showed also that our patients had continuous hyperglycemia, except for the specimen of blood taken during fasting There was no ketosis Our patients presented no symptoms, and their loss of weight was not significant From these observations we feel that the clinical features offer a more satisfactory guide to good therapy than the chemical determinations on the blood and urine We feel that if with a speci-

¹⁷ Tolstoi, E, and Walton, M Unpublished data

¹⁸ MacLeod, J J R The Fuel of Life, Princeton, N J, Princeton University Press, 1928, p 58

fied quantity of protamine insulin the patient is symptom free, has no ketonuria, maintains his weight and a good state of nutrition and is able to be socially useful, the desiderata of adequate control have been fulfilled, even though glycosuria and hyperglycemia are present. And since dividing the diet unequally has not altered the situation materially it is our policy to simplify the treatment as much as possible. We recommend, therefore, an adequate caloric diet and one dose of protamine insulin sufficient to maintain the patient's weight at an optimum and more or less constant level. We recommend also that the urine be free from ketone bodies, but glycosuria is not only permitted but desirable, since it offers protection from insulin reactions. Why patients on such a regimen do well is a matter for speculation. It is our thought that, provided each patient metabolizes a quantity of carbohydrate essential for his particular metabolic needs, the excess may be excreted without damaging results.

SUMMARY

Two patients with severe diabetes were carefully observed for fifty and sixty days respectively in the metabolism service. Both patients were young women. Their caloric intake was constant at 1,640 calories, and each received a single dose of protamine zinc insulin in the morning. In one case the dose was 50 and in the other 60 units. The composition of the diet was 75 Gm of protein, 60 Gm of fat and 200 Gm of carbohydrate for the first thirty days, and this diet was divided into equal portions at times ($\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$) and into unequal portions at other periods. After this thirty day period the diet was changed to 75 Gm of protein, 105 Gm of fat and 100 Gm of carbohydrate. This reduced the carbohydrate by one-half, but the total calories were kept constant by increasing the fat. Equal and unequal fractionation of this diet also was employed. The dose of insulin was always kept the same, and the effects of these procedures were observed. It was noted that the patients excreted an average of 100 Gm of dextrose daily during the first experimental thirty day period. It was observed also that in spite of this glycosuria they were remarkably free from any and all symptoms of diabetes and then loss of weight was no greater than could be accounted for by their diet, which was subcaloric for them as judged by the Aub-Du Bois standards. The nitrogen equilibrium of the patients was maintained. Their urine was free from ketone bodies. Equal or unequal division of the diets was of no consequence in relation to the glycosuria. Decreasing the carbohydrate by 100 Gm and increasing the fat resulted in a diminution of the glycosuria, but the utilization of the dextrose also was diminished. With the lower carbohydrate diet also there was little difference in the dextrose output, whether the diet was equally or unequally divided. The sugar curves through the day revealed normal

and approximately normal values before breakfast only. During the remainder of the day there was persistent hyperglycemia irrespective of the type of diet or its division.

CONCLUSIONS

1. When protamine zinc insulin is used to treat diabetes the glycosuria is not materially influenced by dietary shifts from equal to unequal portions.

2. With protamine zinc insulin, the glycosuria was diminished by a lower carbohydrate diet, but the utilization of dextrose was greater with the higher carbohydrate diets.

3. For patients treated with protamine zinc insulin the guiding feature of satisfactory treatment should be the maintenance of weight, freedom from symptoms and absence of ketone bodies in the urine. Glycosuria is desirable, as it affords protection from reactions.

TOTAL DIFFERENTIAL AND ABSOLUTE LEUKOCYTE COUNTS AND SEDIMENTATION RATES

DETERMINED FOR HEALTHY PERSONS NINETEEN YEARS
OF AGE AND OVER

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INEZ E BROWNLEE, B A

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It is the purpose of this article to supply more accurate data than have heretofore been available for total, differential and absolute leukocyte counts and sedimentation rates of healthy adults 19 years of age and over. This is one of a series of papers on hematologic standards for healthy persons from birth through adult life. The data for other age groups has been or will be reported here and elsewhere.¹

From the Department of Medicine, University of Oregon Medical School

1 (a) Osgood, E E Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch Int Med **37** 685-706 (May) 1926 (b) Osgood, E E, and Haskins, H D Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, *ibid* **39** 643-655 (May) 1927 (c) Osgood, E E, and Baker, R L Erythrocyte, Hemoglobin, Cell Volume, and Color, Volume and Saturation Index Standards for Normal Children of School Age, Am J Dis Child **50** 343-358 (Aug) 1935 (d) Osgood, E E Normal Hematologic Standards, Arch Int Med **56** 849-863 (Nov) 1935 (e) Osgood, E E, Baker, R L, Brownlee, I E Osgood, M W, Ellis, D M, and Cohen, W Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children Four to Seven Years of Age, Am J Dis Child **58** 61 (July) 1939, (f) Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children Eight to Fourteen Years of Age, *ibid*, to be published (g) Osgood, E E, and others Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Adolescents Fifteen to Eighteen Years of Age, J Lab & Clin Med, to be published (h) Chumard, E G, Osgood, E E, and Ellis, D M Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Newborn Infants, to be published (i) Chumard, E G, Osgood, E E, and Ellis, D M Erythrocyte, Hemoglobin, Cell Volume, and Color, Volume and Saturation Index Standards for Healthy Newborn Infants, to be published (j) Osgood, E E, and others Erythrocyte, Hemoglobin,

(Footnote continued on next page)

The values given in most textbooks appear to have been copied from one book to another since the very early studies. Apparently no attention has been paid to the study by Galambos² in 1912 or to the studies of Torday³ and Miller,⁴ who obtained similar results. Figures obtained by recent studies⁵ of healthy persons in various parts of the world also disagree with the textbook figures, but the differences were interpreted as probably due to climate, altitude or race. Actually, the results agree well with those of Galambos² and with those reported here. Results of studies of the variability of leukocyte counts⁶ in which many counts

Cell Volume, and Color, Volume and Saturation Index Standards for Healthy Adolescent Males, Fifteen Years of Age and Over, to be published, (*k*) Erythrocyte, Hemoglobin, Cell Volume, and Color, Volume and Saturation Index Standards for Healthy Females, Fifteen years of Age and Over, to be published, (*l*) Reticulocyte Counts in Healthy Newborn Infants, to be published, (*m*) Icterus Index Determinations in Healthy Newborn Infants, to be published, (*n*) Reticulocyte Counts in Healthy Adolescent Boys and Girls, to be published

2 Galambos, A. Ueber das normale qualitative Blutbild, *Folia haemat* **13** 153-159 (April) 1912

3 Torday, A. Vom normalen qualitativen Blutbild, *Virchows Arch f path Anat* **213** 529-536 (July) 1913

4 Miller, S. R. The Normal Differential Leucocyte Count, *Bull Johns Hopkins Hosp* **25** 317-322 (Oct) 1914

5 Stammers, A. D. The Polymorphonuclear-Lymphocyte Ratio at an Altitude of 5,750 Feet, *J Physiol* **78** 335-338 (June 12) 1933. Peterson, R. F., and Peterson, W. G. The Differential Count at High Altitudes, *J Lab & Clin Med* **20** 723-726 (April) 1935. Kennedy, W. P., and Mackay, I. The Normal Leucocyte Picture in a Hot Climate, *J Physiol* **87** 336-344 (Sept 8) 1936. Gansslen, M. Regionale Verschiedenheiten des normalen weissen Blutbildes, *Deutsche med Wchnschr* **63** 505-507 (March 26) 1937

6 Feinblatt, H. M. Alimentary Leukocytosis in Eighty Normal Men. A Study in Reference to the Crise Hemoclasique of Widal, *J A M A* **80** 613-615 (March 3) 1923. Sabin, F. R., Cunningham, R. S., Doan, C. A., and Kindwall, J. A. The Normal Rhythm of the White Blood Cells, *Bull Johns Hopkins Hosp* **37** 14-67 (July) 1925. Doan, C. A., and Zerfas, L. G. The Rhythmic Range of the White Blood Cells in Human, Pathological Leucopenic and Leucocytic States, with a Study of Thirty-Two Human Bone Marrows, *J Exper Med* **46** 511-539 (Sept) 1927. Shaw, A. F. B. The Diurnal Tides of the Leucocytes of Man, *J Path & Bact* **30** 1-19 (Jan) 1927. Smith, C., and McDowell, A. M. Normal Rhythm of White Blood Cells in Women, *Arch Int Med* **43** 68-84 (Jan) 1929. Medlar, E. M. The Extent of Variations in the Leukocytes of Normal Individuals, *Am J M Sc* **177** 72-87 (Jan) 1929. Martin, H. E. Physiologic Leucocytosis. The Variation in the Leucocyte Count During Rest and Exercise, and After the Hypodermic Injection of Adrenaline, *J Physiol* **75** 113-129 (June 29) 1932. Lawrence, J. S., Stephens D. J., and Jones, E. Studies in the Normal Human White Blood Cell Picture. II. The Effect of Digestion on the White Blood Cells, *Am J Physiol* **106** 309-313 (Nov) 1933. Kennon, B. R., III, Shipp, M. E., and Hetherington, D. C. A Study of the White Blood Cell Picture in Six Young Men, *ibid* **118** 690-696 (April) 1937

were made for a few subjects also agree better with our results and those of Galambos than with the textbook figures Garrey and Bryan⁷ recently reviewed the literature on total leukocyte counts Bryan, Chastain and Garrey⁸ showed that there is a lower and less variable leukocyte count under basal conditions, but Schweizer⁹ was unable to confirm these findings, and it is hardly practicable to do leukocyte counts only under basal conditions in clinical practice

In many papers on the leukocyte count in disease it is concluded that lymphocytosis or leukopenia occurs because the counts in the disease studied differ from the textbook figures, although they are well within the normal limits here defined

SUBJECTS

All of the subjects lived in or near Portland, Ore, at an elevation of less than 500 feet All were white and nativeborn, in most cases of nativeborn parents The women were chiefly nurses from the staff of Multnomah County Hospital and technicians from the laboratory of the University of Oregon Medical School The men were mostly medical students, with a few interns and physicians All felt well at the time the blood was drawn and had had a recent physical examination All persons over 19 years of age were grouped together because the scatter diagrams^{1d} showed no significant differences for the two sexes and no marked variation with age in this group Few persons over 30 years of age were studied, so that these results can be strictly applied only to persons 19 to 30 years of age It seems probable, however, that the values will prove relatively constant throughout adult life

METHODS

Since the methods used have been described in detail elsewhere,¹⁰ they will be only commented on here Venous blood mixed with 2 mg of dry potassium oxalate per cubic centimeter was used for all determinations, this method is recommended because it is more convenient and accurate than use of blood from the finger or ear The blood was taken at any time of day, as in ordinary office practice

The leukocyte counts were made by skilled technicians using Levy-Neubauer counting chambers and Thoma pipets An area of 4 sq mm was counted, with all the precautions outlined by Osgood¹¹ The differential cell counts were made on Wright's stained smears on glass slides Buffer phosphate was used as a diluent The details of smearing and of staining are described elsewhere¹²

7 Garrey, W E, and Bryan, W R Variations in White Blood Cell Counts, *Physiol Rev* **15** 597-638 (Oct) 1935

8 Bryan, W R, Chastain, L L, and Garrey, W E The Leucocyte Count of Young Male Adults Observed After a Period of Rest and During Mild Activity in the Early Morning, *Am J Physiol* **113** 430-440 (Oct) 1935

9 Schweizer, M The "Basal Level" of the White Cell Count in Man, *Am J Physiol* **105** 217-219 (July 1) 1933

10 Osgood, E E A Textbook of Laboratory Diagnosis, ed 2, Philadelphia, P Blakiston's Son & Co, 1935, pp 409-415 and 430-432

11 Osgood,¹⁰ p 409

12 Osgood, E E, and Ashworth, C M Atlas of Hematology, San Francisco, J W Stacey, Inc, 1937, p 8

TABLE 1—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Adults Nineteen Years Old *

Leuko cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	%	Per		%	Per		%	Per		%	Per		%	Per		%	Per		%	Per		15 Min	45 Min	
		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm			Cu
56	18	27	0.06	1	0.06	0.11	2	0.11	0.06	1	0.06	10	2.2	1	0.22	1	0.22	1	0.22	1	0.22	10	35	
61	57	35	0	0	0	0.18	3	0.18	0	0	0	17	2.3	3	0.18	0	0.18	0	0.18	0	0.18	0	0	
61	46	28	0	0	0	0.06	1	0.06	0.06	1	0.06	16	2.8	1	0.24	2	0.24	2	0.24	2	0.24	15	20	
64	50	32	0	0	0	0	1	0.06	0	0	0	10	2.6	9	0.58	0	0.58	0	0.58	0	0.58	10	20	
66	51	34	0	0	0	0.07	1	0.07	0	0	0	45	3.0	3	0.20	0	0.20	0	0.20	0	0.20	0	0	
66	40	26	0	0	0	0.07	1	0.07	0.07	1	0.07	48	3.2	7	0.46	5	0.46	5	0.46	5	0.46	10	10	
67	47	31	0.13	2	0.13	0.13	2	0.13	0.07	1	0.07	39	2.6	1	0.07	8	0.07	8	0.07	8	0.07	0.5	20	
67	51	34	0.07	1	0.07	0.20	3	0.20	0	0	0	37	2.5	6	0.10	2	0.10	2	0.10	2	0.10	0.5	30	
68	66	45	0	0	0	0	0	0	0.07	1	0.07	30	2.0	3	0.20	0	0.20	0	0.20	0	0.20	0.2	20	
70	50	35	0.07	1	0.07	0.11	2	0.11	0	0	0	1	3.0	2	0.11	2	0.11	2	0.11	2	0.11	1.5	45	
70	31	21	0.07	1	0.07	0	0	0	0.07	1	0.07	57	3.1	7	0.19	0	0.19	0	0.19	0	0.19	0.5	15	
78	40	31	0	0	0	0.08	1	0.08	0.16	2	0.16	31	1.0	1	0.31	2	0.31	2	0.31	2	0.31	0.5	10	
79	41	35	0.08	2	0.08	0.16	2	0.16	0	0	0	10	1.2	10	0.79	2	0.79	2	0.79	2	0.79	0.5	35	
86	41	38	0	0	0	0.17	2	0.17	0	0	0	19	1.2	2	0.17	3	0.17	3	0.17	3	0.17	0.5	10	
91	36	30	0	0	0	0.18	1	0.18	0.09	1	0.09	1	1.9	1	0.36	1	0.36	1	0.36	1	0.36	0.5	15	
105	6	66	0	0	0	0	0	0	0	0	0	21	3.0	8	0.81	0	0.81	0	0.81	0	0.81	10	70	
Average	7.22	17.9	0.5	0.5	0.5	0.10	1.4	0.10	0.04	0.6	0.04	12.5	2.09	1.8	0.5	1.9	0.5	1.9	0.5	1.9	0.5	0.6	22	
Maximum	10.7	66	0.1	2	0.1	0.20	6	0.20	0.16	2	0.16	37	1.9	10	0.84	8	0.84	8	0.84	8	0.84	1.5	70	
Minimum	5.6	31	0	0	0	0	0	0	0	0	0	21	2.0	1	0.07	0	0.07	0	0.07	0	0.07	0	0	
Women																								
50	54	27	0.05	1	0.05	0.05	1	0.05	0	0	0	12	2.1	2	0.10	0	0.10	0	0.10	0	0.10	10	30	
51	15	21	0.11	0	0.11	0	0	0	0.03	0	0.03	18	2.6	1	0.22	0	0.22	0	0.22	0	0.22	15	90	
61	52	22	0	0	0	0	0	0	0	0	0	16	2.8	2	0.12	0	0.12	0	0.12	0	0.12	10	100	
69	69	48	0	0	0	0.07	1	0.07	0	0	0	26	1.8	3	0.21	0	0.21	0	0.21	0	0.21	20	150	
70	51	36	0	0	0	0.07	1	0.07	0	0	0	18	3.4	0	0	0	0	0	0	0	0	30	100	
71	45	32	0.11	1	0.11	0.07	1	0.07	0.07	1	0.07	30	3.6	1	0.07	0	0.07	0	0.07	0	0.07	10	50	
72	64	46	0	0	0	0.07	1	0.07	0	0	0	11	2.2	4	0.29	0	0.29	0	0.29	0	0.29	0.5	200	
73	41	32	0	0	0	0.15	2	0.15	0.22	3	0.22	16	2.1	5	0.36	0	0.36	0	0.36	0	0.36	10	100	
74	55	26	0	0	0	0	0	0	0	0	0	59	4.1	6	0.44	0	0.44	0	0.44	0	0.44	50	100	
76	29	22	0.08	1	0.08	0.08	1	0.08	0	0	0	19	3.7	5	0.38	11	0.38	11	0.38	11	0.38	0	60	
79	40	32	0	0	0	0.47	0	0.47	0	0	0	42	3.3	11	0.87	0	0.87	0	0.87	0	0.87	20	70	
80	62	50	0	0	0	0.08	1	0.08	0.16	2	0.16	32	2.6	3	0.24	0	0.24	0	0.24	0	0.24	30	210	
82	63	52	0	0	0	0	0	0	0	0	0	35	2.9	2	0.16	0	0.16	0	0.16	0	0.16	40	250	
84	19	41	0	0	0	0	0	0	0	0	0	1	3.6	1	0.08	7	0.08	7	0.08	7	0.08	10	60	
84	66	55	0.25	2	0.25	0.17	2	0.17	0.08	1	0.08	22	1.8	6	0.50	0	0.50	0	0.50	0	0.50	20	150	
86	76	65	0	0	0	0	0	0	0	0	0	21	1.8	3	0.26	0	0.26	0	0.26	0	0.26	20	110	
115	75	86	0	0	0	0.23	2	0.23	0	0	0	11	1.6	9	1.01	0	1.01	0	1.01	0	1.01	15	80	
Average	7.53	41.5	0.6	0.6	0.6	0.09	1.1	0.09	0.03	0.7	0.03	38.5	2.80	3.9	0.31	1.2	0.31	1.2	0.31	1.2	0.31	18	112	
Maximum	11.5	76	0.25	6	0.25	0.17	6	0.17	0.22	3	0.22	59	4.1	11	1.01	14	1.01	14	1.01	14	1.01	50	250	
Minimum	5.0	22	0	0	0	0	0	0	0	0	0	11	1.6	0	0	0	0	0	0	0	0	0	30	
Men and Women																								
722	47.9	3.16	0.5	0.5	0.5	0.10	1.1	0.10	0.04	0.6	0.04	12.8	2.09	4.8	0.35	1.9	0.35	1.9	0.35	1.9	0.35	0.6	22	
753	54	41.5	0.6	0.6	0.6	0.09	1.1	0.09	0.03	0.5	0.03	35	2.80	3.9	0.31	1.2	0.31	1.2	0.31	1.2	0.31	18	112	
738	51.1	3.82	0.5	0.5	0.5	0.09	1.3	0.09	0.04	0.5	0.04	10.6	2.94	4.4	0.33	1.5	0.33	1.5	0.33	1.5	0.33	1.3	67	
Maximum	11.5	76	0.25	6	0.25	0.17	6	0.17	0.22	3	0.22	59	4.1	11	1.01	14	1.01	14	1.01	14	1.01	50	250	
Minimum	5.0	22	0	0	0	0	0	0	0	0	0	11	1.6	0	0	0	0	0	0	0	0	0	0	

* In all tables the number per cubic millimeter represents thousands. Neutrophil lobocytes are polymorphonuclears and neutrophil rhabdocytes, staff cells

TABLE 2—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Adults Twenty Years Old *

Leuko- cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate	
	Per		%	Per		%	Per		%	Per		%	Per		%	Per		%	Per		Cu Mm	15 Min	45 Min
	Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm			
15	52	23		0	0		0	0		0	0		41	20		4	0.18		0	0		?	?
52	74	38		2	0.10		0	0.10		0	0		20	10		2	0.10		0	0		10	60
56	47	26		0	0		3	0.17		0	0		42	21		8	0.45		0	0		0.5	50
57	59	34		5	0.28		0	0		0	0.06		32	18		2	0.11		0	0		0.2	20
67	69	16		0	0		1	0.07		0	0		24	16		6	0.40		0	0		0.1	10
67	50	34		0	0		5	0.31		0	0.07		35	23		9	0.60		0	0		10	60
68	54	27		0	0		1	0.27		0	0		34	23		8	0.54		0	0		15	15
68	26	24		0	0		1	0.07		1	0.07		54	37		2	0.14		0	0.41		50	370
70	53	39		0	0		2	0.11		0	0		40	28		3	0.21		0	0		10	15
72	49	35		0	0		1	0.29		0	0		41	32		3	0.22		0	0		0.5	20
72	61	41		0	0		1	0.07		0	0		33	24		5	0.36		0	0		?	?
73	39	28		0	0		2	0.15		0	0		37	42		2	0.15		0	0		0	10
74	69	51		2	0.15		3	0.22		0	0		23	17		3	0.22		0	0		0.5	20
76	72	55		0	0		1	0.08		0	0		24	18		3	0.23		0	0		0.5	25
78	38	45		0	0		0	0		0	0		38	34		4	0.31		0	0		10	10
94	56	53		0	0		1	0.09		0	0		42	39		1	0.09		0	0		0.5	20
102	51	52		0	0		4	0.41		0	0		38	39		7	0.71		0	0		1.5	90
Average	701	39		0.5	0.03		2	0.14		0.2	0.01		36.7	259		12	0.30		0.4	0.02		0.9	53
Maximum	102	55		5	0.28		5	0.41		1	0.07		57	42		9	0.71		6	0.41		3.0	370
Minimum	45	23		0	0		0	0		0	0		20	10		1	0.09		0	0		0	10
Women																							
54	59	32		0	0		1	0.05		0	0		31	17		8	0.43		0	0		10	50
57	56	32		5	0.28		3	0.17		0	0		36	21		0	0		0	0		40	350
58	60	35		0	0		1	0.23		0	0		28	16		8	0.46		0	0		2.5	190
62	59	37		0	0		9	0.56		0	0		24	15		8	0.49		0	0		20	160
66	48	32		0	0		1	0.07		0	0		30	30		5	0.33		0	0		0.5	10
67	37	25		1	0.07		0	0		2	0.13		58	39		2	0.13		0	0		10	30
72	54	39		1	0.29		1	0.07		0	0		38	27		3	0.22		0	0		20	160
86	30	26		0	0		8	0.69		0	0		58	50		4	0.34		0	0		20	230
95	39	37		1	0.10		0	0		1	0.10		56	53		3	0.28		0	0		10	10
102	49	50		1	0.10		0	0		0	0		47	46		4	0.41		0	0		10	70
104	73	76		1	0.10		3	0.31		2	0.21		14	15		7	0.73		0	0		15	120
105	73	77		2	0.21		4	0.42		0	0		19	20		1	0.10		0	0		30	250
106	35	37		2	0.21		2	0.21		0	0		61	65		0	0		0	0		20	120
Average	795	412		1.3	0.10		2.8	0.21		0.4	0.03		39.5	318		4.1	0.30		0	0		18	137
Maximum	106	77		5	0.29		9	0.69		2	0.21		61	65		8	0.73		0	0		10	350
Minimum	54	25		0	0		0	0		0	0		14	15		0	0		0	0		0.5	10
Men and Women																							
701	55.9	390		0.5	0.03		2	0.14		0.2	0.01		36.7	259		4.2	0.30		0.4	0.02		0.9	53
795	51.7	412		1.3	0.10		2.8	0.21		0.4	0.03		39.5	318		4.1	0.30		0	0		18	137
742	54.1	399		0.9	0.03		2.3	0.18		0.3	0.02		37.9	285		4.2	0.30		0.2	0.11		1.3	91
106	71	77		5	0.29		9	0.69		2	0.21		61	65		9	0.73		6	0.41		50	370
15	30	23		0	0		0	0		0	0		14	10		0	0		0	0		00	10

* See footnote, table 1

TABLE 3—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Adults Twenty-One Years Old *

Leuko cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	Per		Men	Per		Men	Per		Men	Per		Men	Per		Men	Per		Men	Per		Men	Per		Men
	%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm	
46	68	31	0	0	0	0	2	0.09	1	0.05	28	13	1	0.05	0	0	0	0	0	0	10	10	10	
49	26	13	1	0.05	0	0	3	0.15	1	0.05	67	33	2	0.10	0	0	0	0	0	0	0.5	10	10	
52	15	23	3	0.16	0	0	1	0.05	2	0.10	48	25	1	0.05	0	0	0	0	0	0	10	15	15	
52	30	16	2	0.10	0	0	0	0	2	0.10	65	34	1	0.05	0	0	0	0	0	0	0	10	10	
54	51	28	0	0	0	0	2	0.11	2	0.11	43	23	2	0.11	0	0	0	0	0	0	0.5	20	20	
56	49	27	0	0	0	0	1	0.06	1	0.06	43	24	6	0.34	0	0	0	0	0	0	10	30	30	
56	60	34	0	0	0	0	2	0.11	0	0	36	20	2	0.11	0	0	0	0	0	0	0	10	10	
57	62	35	0	0	0	0	0	0	1	0.06	35	20	2	0.11	0	0	0	0	0	0	10	50	50	
59	33	19	0	0	0	0	0	0	0	0	57	34	2	0.12	8	0.47	0	0	0	0	10	15	15	
60	57	34	1	0.06	0	0	5	0.30	1	0.06	29	17	7	0.42	0	0	0	0	0	0	0	0	0	0
61	42	26	5	0.30	0	0	1	0.06	1	0.06	39	24	12	0.73	0	0	0	0	0	0	10	90	90	
61	56	34	1	0.06	0	0	3	0.18	2	0.12	25	15	7	0.43	6	0.37	0	0	0	0	10	30	30	
62	37	23	0	0	0	0	2	0.12	0	0	48	30	0	0	11	0.68	0	0	0	0.5	20	20	20	
62	70	43	0	0	0	0	2	0.12	0	0	26	16	2	0.12	0	0	0	0	0	0	0.5	10	10	
64	65	42	0	0	0	0	0	0	0	0	29	19	6	0.38	0	0	0	0	0	0	0.5	20	20	
64	33	21	1	0.06	0	0	6	0.38	0	0	76	36	4	0.26	0	0	0	0	0	0	0	10	10	10
64	46	29	0	0	0	0	1	0.06	0	0	43	28	4	0.26	6	0.38	0	0	0	0	10	20	20	
64	65	42	1	0.06	0	0	2	0.13	0	0	31	20	1	0.06	0	0	0	0	0	0	10	40	40	
65	53	34	1	0.06	0	0	1	0.06	0	0	40	26	5	0.32	0	0	0	0	0	0	0.1	0.5	0.5	0.5
66	46	30	0	0	0	0	3	0.20	0	0	43	28	1	0.07	7	0.46	0	0	0	0	10	15	15	15
67	48	32	6	0.40	0	0	1	0.07	0	0	11	27	4	0.27	0	0	0	0	0	0	10	110	110	
68	48	33	2	0.14	0	0	2	0.14	0	0	42	29	6	0.41	0	0	0	0	0	0	0.5	10	10	10
68	60	41	0	0	0	0	2	0.14	0	0	35	24	3	0.20	0	0	0	0	0	0	0.5	20	20	20
70	42	29	2	0.14	0	0	3	0.21	0	0	45	32	8	0.56	0	0	0	0	0	?	?	?	?	?
71	55	39	0	0	0	0	1	0.07	0	0	36	26	8	0.57	0	0	0	0	0	0	0.5	25	25	25
72	63	45	0	0	0	0	1	0.07	1	0.07	31	22	4	0.29	0	0	0	0	0	0	10	50	50	50
72	47	34	0	0	0	0	4	0.29	1	0.07	45	32	3	0.22	0	0	0	0	0	0	0.5	30	30	30
74	51	38	0	0	0	0	2	0.15	1	0.07	39	29	7	0.52	0	0	0	0	0	?	?	?	?	?
76	46	35	0	0	0	0	3	0.23	0	0	50	38	1	0.08	0	0	0	0	0	0	10	15	15	15
76	66	50	0	0	0	0	0	0	1	0.08	25	19	8	0.61	0	0	0	0	0	0	10	20	20	20

77	58	45	0	0	1	0.08	1	0.08	37	28	3	0.23	0	0	0.5	20
78	61	48	0	0	0	0	0	0	37	29	2	0.16	0	0	1.0	50
79	13	34	0	0	5	0.40	2	0.16	46	36	3	0.24	0	0	0	10
82	60	19	1	0.08	0	0	1	0.08	34	28	4	0.33	0	0	0.5	20
84	19	11	0	0	1	0.08	1	0.08	49	41	0	0	0	0	0.5	10
86	52	45	0	0	0	0	4	0.34	40	34	4	0.34	0	0	0.5	10
92	40	37	1	0.09	4	0.37	0	0	51	47	4	0.37	0	0	1.0	60
108	62	67	0	0	2	0.22	0	0	30	32	6	0.65	0	0	?	?
122	65	79	7	0.85	2	0.24	1	0.12	21	26	4	0.49	0	0	1.0	10
Average	691	36	0.9	0.07	18	0.13	0.7	0.05	101	273	38	0.27	1.0	0.06	0.7	26
Maximum	122	79	7	0.85	6	0.40	4	0.34	67	17	12	0.73	11	0.68	1.0	110
Minimum	16	11	0	0	0	0	0	0	21	11	0	0	0	0	0	0
Women																
19	18	24	8	0.39	0	0	0	0	42	21	2	0.10	0	0	1.5	130
50	67	34	0	0	0	0	0	0	29	14	4	0.20	0	0	5.0	200
52	60	31	5	0.25	0	0	2	0.10	33	17	0	0	0	0	1.5	70
64	79	18	0	0	1	0.06	2	0.13	32	20	6	0.38	0	0	1.5	180
74	67	50	2	0.15	1	0.30	0	0	17	13	3	0.22	7	0.52	2.0	110
76	44	33	2	0.15	1	0.08	1	0.08	51	39	1	0.08	0	0	3.0	210
84	76	17	0	0	2	0.17	0	0	27	23	2	0.17	13	1.09	0.5	40
92	63	38	8	0.71	1	0.09	0	0	26	24	2	0.18	0	0	2.0	90
92	43	10	0	0	3	0.28	0	0	44	40	10	0.92	0	0	0.5	30
132	81	110	2	0.26	0	0	0	0	11	18	1	0.13	0	0	1.0	50
Average	765	165	27	0.20	12	0.10	0.5	0.03	315	229	71	0.24	2	0.16	18	113
Maximum	132	110	8	0.74	4	0.30	2	0.13	51	40	10	0.92	13	1.09	5.0	210
Minimum	49	24	0	0	0	0	0	0	14	13	0	0	0	0	0.5	30
Men and Women																
691	515	36	0.9	0.07	18	0.13	0.7	0.05	401	273	38	0.27	0.1	0.06	0.7	26
765	79	165	27	0.20	12	0.10	0.5	0.03	315	229	71	0.24	2	0.16	18	113
Average	716	182	13	0.09	17	0.12	0.7	0.05	384	264	37	0.26	1.2	0.08	0.9	15
Maximum	132	110	8	0.85	6	0.40	4	0.14	67	17	12	0.92	13	1.09	5.0	210
Minimum	16	11	0	0	0	0	0	0	14	13	0	0	0	0	0	0

* See footnote table 1

TABLE 4—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Adults Twenty-Two Years Old *

Leuko- cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	%	Per		%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	15 Min	45 Min	
		Mm	%																					
47	55	26	0	1	0.05	0	0	0.10	0	0	0.10	13	20	1	0.05	0	0	0	0	0	0.5	15		
50	36	18	2	3	0.15	2	0	0	0	0	0	55	28	2	0.10	0	0	0	0	0	0.5	15		
56	45	25	0	2	0.11	0	0	0	0	0	0	51	29	2	0.11	0	0	0	0	0	0.5	30		
57	53	30	1	2	0.11	0	0	0	0	0	0	36	21	8	0.46	0	0	0	0	0	1.0	30		
58	67	39	2	5	0.29	0	0	0	0	0	0	22	13	1	0.23	0	0	0	0	0	1.0	40		
60	11	25	0	3	0.30	0	0	0.12	2	0	0	12	25	3	0.15	7	0.42	0	0	0	0.5	20		
63	56	35	0	0	0	0	0	0	0	0	0	34	21	9	0.37	0	0	0	0	0	0.5	20		
64	60	38	1	0	0	0	0	0	0	0	0	34	22	3	0.19	0	0	0	0	0	1.0	40		
64	52	33	0	6	0.38	0	0	0	0	0	0	10	26	2	0.13	0	0	0	0	0	0.5	20		
65	56	36	0	2	0.13	0	0	0	0	0	0	10	26	2	0.13	0	0	0	0	0	0.5	20		
68	46	31	5	2	0.14	0	0	0	0	0	0	11	30	3	0.20	0	0	0	0	0	1.0	46.0		
68	43	29	0	2	0.20	0	0	0	0	0	0	17	47	7	0.48	0	0	0	0	0	0.5	20		
70	32	22	1	0	0	0	0	0	0	0	0	67	47	0	0	0	0	0	0	0	0	30		
70	66	46	0	0	0	0	1	0.07	0	0.07	0	30	21	3	0.21	0	0	0	0	0	0.5	15		
71	58	43	0	2	0.15	0	1	0.07	1	0.07	0	31	21	8	0.59	0	0	0	0	0	0.5	20		
74	68	50	0	1	0.07	0	1	0.07	1	0.07	0	24	18	6	0.11	0	0	0	0	0	0.2	20		
76	58	44	0	0	0	0	1	0.08	1	0.08	0	11	31	9	0.70	0	0	0	0	0	0.5	10		
78	37	37	0	0	0	0	0	0	0	0	0	1	27	2	0.16	0	0	0	0	0	0.5	20		
78	71	42	1	1	0.08	0	1	0.08	1	0.08	0	32	25	2	0.17	0	0	0	0	0	1.0	25		
79	69	55	0	0	0	0	0	0	0	0	0	25	22	6	0.16	0	0	0	0	0	0	10		
80	60	48	0	0	0	0	0	0	0	0	0	3	30	2	0.16	0	0	0	0	0	0.5	20		
81	45	36	0	2	0.08	0	1	0.08	1	0.08	0	10	32	6	0.49	0	0	0	0	0	1.0	24		
84	62	52	0	1	0.16	0	0	0	0	0	0	33	27	2	0.16	0	0	0	0	0	0.5	20		
84	62	52	0	2	0.17	0	2	0.17	2	0.17	0	27	27	7	0.49	0	0	0	0	0	1.0	25		
89	14	39	0	7	0.18	0	0	0	0	0	0	11	39	10	0.89	0	0	0	0	0	0	10		
92	48	38	1	1	0.09	0	0	0	0	0	0	16	32	7	0.37	0	0	0	0	0	1.0	20		
96	53	43	0	0	0	0	0	0	0	0	0	18	33	1	0.27	0	0	0	0	0	0.5	20		
97	47	46	0	0	0.10	0	0	0	0	0	0	16	32	7	0.67	0	0	0	0	0	0.5	20		
100	51	51	1	1	0.10	0	0	0	0	0	0	17	32	7	0.18	0	0	0	0	0	?	?		
104	68	71	1	0	0	0	0	0	0	0	0	10	16	1	0.40	0	0	0	0	0	?	?		
114	79	90	1	1	0.11	0	0	0	0	0	0	28	29	1	0.31	0	0	0	0	0	1.0	50		
Average	76	116	0.5	1.5	0.11	0.1	0.1	0.0	0.1	0.0	0.0	38.1	28.0	1.1	0.33	0.6	0.01	0.01	0.01	0.01	1.6	57		
Maximum	114	90	5	7	0.38	2	2	0.17	2	0.17	0	67	37	10	0.89	7	0.55	0.55	0.55	0.55	1.6	46.0		
Minimum	47	18	0	0	0	0	0	0	0	0	0	15	13	0	0	0	0	0	0	0	0	1.0		
Women																								
46	61	28	0	1	0.05	0	0	0.06	0	0	0.06	29	13	9	0.11	0	0	0	0	0	0.90	29.0		
56	63	35	1	3	0.17	0	0	0	0	0	0	29	16	4	0.22	0	0	0	0	0	1.0	30		
61	51	31	2	0	0	0	1	0.06	0	0	0	42	26	4	0.21	0	0	0	0	0	0.5	40		
62	37	23	0	1	0.25	0	0	0	0	0	0	53	33	6	0.37	0	0	0	0	0	0.5	35		
67	41	23	0	0	0.25	0	0	0	0	0	0	52	35	1	0.27	0	0	0	0	0	1.0	60		
70	56	39	2	2	0.14	0	0	0	0	0	0	27	19	7	0.49	6	0.42	0	0	0	0.60	30.0		
70	58	41	2	1	0.07	0	0	0	0	0	0	30	21	9	0.63	0	0	0	0	0	1.0	30		
82	73	60	2	1	0.08	0	0	0	0	0	0	20	16	4	0.33	6	0	0	0	0	0.50	50		
110	59	65	1	1	0.11	0	1	0.11	1	0.11	0	30	33	8	0.88	0	0	0	0	0	0.30	18.0		
Average	693	39	1.1	1.1	0.10	0.2	0.2	0.02	0.2	0.02	0.02	34.7	24.6	6.1	0.43	0.7	0.05	0.05	0.05	0.05	1.6	11.8		
Minimum	46	23	0	0	0	0	0	0	0	0	0	20	13	1	0.22	0	0	0	0	0	0.5	30		
Men and Women																								
76	54.2	41.6	0.5	1.8	0.13	0.4	0.4	0.03	0.4	0.03	0.03	38.1	28.6	4.3	0.33	0.6	0.04	0.04	0.04	0.04	1.6	57		
693	55.8	39	1.1	1.4	0.10	0.2	0.2	0.02	0.2	0.02	0.02	34.7	23.6	6.1	0.43	0.7	0.05	0.05	0.05	0.05	1.6	11.8		
715	54.5	41	0.6	1.7	0.12	0.1	0.1	0.03	0.1	0.03	0.03	37.1	27.5	4.7	0.35	0.6	0.04	0.04	0.04	0.04	1.8	7.1		
Maximum	114	90	5	7	0.38	2	2	0.17	2	0.17	0	67	37	10	0.89	7	0.55	0.55	0.55	0.55	1.8	46.0		
Minimum	46	32	0	0	0	0	0	0	0	0	0	18	13	0	0	0	0	0	0	0	0	1.0		

* See footnote, table 1

TABLE 5—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Men Twenty-Three Years Old*

Leuko cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	%	Per		%	Per		%	Per		%	Per		%	Per		%	Per		%	Per		%	Per	
		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm
14	70	31	0	0	0	0	0	0	0	0	0	0	22	10	6	0.26	2	0.09	0	0	2	10	10	
50	60	30	1	0.05	1	0.05	1	0.05	1	0.05	0	0	31	16	6	0.30	0	0	0	0	0	0	10	
50	38	19	1	0.05	5	0.25	5	0.25	0	0	0	0	33	26	2	0.10	0	0	0	0	0	0	10	
52	62	32	1	0.05	1	0.05	1	0.05	0	0	0	0	30	16	6	0.31	0	0	0	0	0	20	70	
52	43	22	3	0.16	0	0	0	0	0	0	0	0	39	20	5	0.26	10	0.12	0	0	0	0	20	
53	38	20	3	0.16	7	0.37	7	0.37	2	0.11	0	0	46	24	1	0.21	0	0	0	0	0	10	50	
54	64	41	0	0	0	0	0	0	0	0	0	0	31	18	2	0.11	0	0	0	0	0	0	10	
62	53	33	0	0	0	0	0	0	0	0	0	0	46	29	1	0.06	0	0	0	0	0	0	15	
64	63	40	1	0.06	1	0.06	1	0.06	0	0	0	0	34	22	1	0.06	0	0	0	0	0	0	50	
68	70	34	2	0.14	2	0.14	2	0.14	0	0	0	0	40	27	6	0.41	0	0	0	0	0	15	60	
68	43	29	0	0	0	0	0	0	0	0	0	0	50	34	7	0.48	0	0	0	0	0	?	?	
69	27	19	0	0	9	0.62	9	0.62	1	0.07	0	0	52	36	2	0.14	8	0.55	0	0	8	10	20	
70	47	33	0	0	0	0	0	0	0	0	0	0	48	14	5	0.35	0	0	0	0	0	10	50	
74	67	50	0	0	3	0.22	3	0.22	0	0	0	0	24	18	6	0.44	0	0	0	0	0	0	15	
76	71	54	0	0	8	0.61	8	0.61	0	0	0	0	16	12	5	0.38	0	0	0	0	0	0	10	
79	61	48	1	0.08	0	0	0	0	0	0	0	0	34	27	4	0.32	0	0	0	0	0	20	100	
80	70	40	0	0	2	0.16	2	0.16	1	0.24	0	0	40	32	5	0.40	0	0	0	0	0	0	10	
82	66	51	0	0	3	0.25	3	0.25	1	0.08	0	0	27	22	3	0.25	0	0	0	0	0	0	10	
84	42	35	1	0.08	6	0.50	6	0.50	2	0.17	0	0	46	39	3	0.25	0	0	0	0	0	0	15	
86	47	40	0	0	4	0.34	4	0.34	0	0	0	0	48	41	1	0.09	0	0	0	0	0	10	50	
86	60	52	0	0	1	0.09	1	0.09	0	0	0	0	31	27	8	0.69	0	0	0	0	0	0	20	
95	55	52	0	0	0	0	0	0	0	0	0	0	45	13	0	0	0	0	0	0	0	10	20	
96	57	55	0	0	8	0.77	8	0.77	1	0.10	0	0	32	11	2	0.19	0	0	0	0	0	10	12	
114	63	72	0	0	1	0.11	1	0.11	0	0	0	0	32	36	3	0.34	0	0	0	0	0	10	10	
117	61	74	0	0	0	0	0	0	0	0	0	0	31	36	6	0.70	0	0	0	0	0	20	120	
122	47	57	0	0	3	0.98	3	0.98	0	0	0	0	40	19	5	0.61	0	0	0	0	0	0	10	
Average	749	541	11	0.5	0.03	2.7	0.21	0.4	0.03	0.4	0.03	0.4	37.4	27.9	4.0	0.70	0.8	0.04	0.04	0.04	0.04	0.8	3.1	
Maximum	122	71	7.4	3	0.16	9	0.98	3	0.24	3	0.24	3	53	4.9	8	0.70	10	0.55	0.55	0.55	0.55	2.0	12.0	
Minimum	14	27	1.9	0	0	0	0	0	0	0	0	0	16	1.0	0	0	0	0	0	0	0	0	1.0	

* See footnote, table 1

TABLE 6—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Men Twenty-Four Years Old *

Leuko- cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	Per		%	Per		%	Per		%	Per		%	Per		%	15 Min		45 Min
	Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm	
48	38	18	0	0	0.05	1	0.05	55	2.6	5	0.24	0	0	0	0	?	?	?
54	49	2.6	3	0.16	0.05	0	0.05	40	2.2	6	0.32	0	0	0	0	1.0	11.0	11.0
56	51	2.9	0	0	0.17	0	0.17	13	2.1	3	0.17	0	0	0	0	0.5	1.5	1.5
68	52	3.5	0	0	0.14	0	0.14	41	2.8	5	0.34	0	0	0	0	?	?	?
68	54	3.7	0	0	0.11	1	0.07	39	2.7	1	0.27	0	0	0	0	?	?	?
70	66	4.6	0	0	0	0	0	26	1.8	8	0.56	0	0	0	0	2.0	18.0	18.0
70	56	3.9	1	0.07	0	0	0	41	2.9	2	0.14	0	0	0	0	0.1	1.0	1.0
71	48	3.4	0	0	0	0	0.07	48	3.1	3	0.21	0	0	0	0	0.5	1.0	1.0
76	60	4.6	0	0	0.15	2	0.15	34	2.6	2	0.15	0	0	0	0	0.5	1.0	1.0
78	56	4.1	0	0	0.08	1	0.08	40	3.1	3	0.23	0	0	0	0	0.2	1.5	1.5
81	13	3.5	0	0	0	0	0	50	1.5	1	0.08	0	0	0	0	1.5	6.0	6.0
88	72	6.3	1	0.09	0.18	2	0.18	20	1.8	5	0.14	0	0	0	0	0	1.0	1.0
88	49	1.3	0	0	0.62	7	0.62	40	3.5	1	0.35	0	0	0	0	0.5	3.0	3.0
89	45	4.0	0	0	0.09	1	0.09	51	1.5	2	0.18	0	0	0	0	?	?	?
90	60	5.1	0	0	0.27	3	0.27	35	3.2	2	0.18	0	0	0	0	0	1.0	1.0
100	47	4.7	0	0	0.30	3	0.30	47	1.7	1	0.10	0	0	0	0	2.0	11.5	11.5
124	66	8.2	1	0.12	0.37	3	0.37	19	2.4	11	1.36	0	0	0	0	2.0	5.0	5.0
Average	7.76	53.6	0.4	0.03	0.15	1.8	0.15	39.7	3.01	3.9	0.31	0	0	0	0	0.8	4.8	4.8
Maximum	12.4	72	3	0.16	0.62	7	0.62	56	1.7	11	1.36	0	0	0	0	2.0	18.0	18.0
Minimum	4.8	38	0	0	0	0	0	19	1.8	1	0.08	0	0	0	0	0	1.0	1.0

* See footnote, table 1

TABLE 7—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Men Twenty-Five Years Old *

Leuko- cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	Per		Cu Mm	Per		Cu Mm	Per		Cu Mm	Per		Cu Mm	Per		Cu Mm	Per		Cu Mm	Per		Cu Mm	15 Min		45 Min
	%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm		%	Cu Mm	
44	61	27	0	0	0	0	10	0.41	0	0	0	0	10	0.8	0.41	10	0.41	0	0	0	0	0.5	0	10
51	60	32	0	0	0	0	7	0.38	0	0	0	0	27	1.5	0.32	6	0.32	0	0	0	0	?	?	?
58	50	29	0	0	0	0	1	0.06	0	0	0	0	41	2.6	0.29	5	0.29	0	0	0	0	1.0	7.0	?
58	48	28	0	0	0	0	1	0.06	0	0	0	0	46	2.7	0.29	5	0.29	0	0	0	0	?	?	?
61	35	21	0	0	0	0	3	0.18	1	0.06	0	0	58	3.5	0.18	3	0.18	0	0	0	0	0	1.5	?
61	55	34	2	0.12	0	0	0	0	1	0.06	0	0	40	2.4	0.12	2	0.12	0	0	0	0	1.0	1.0	?
63	64	40	0	0	0	0	2	0.13	0	0	0	0	28	1.8	0.38	6	0.38	0	0	0	0	1.0	2.0	?
64	45	20	0	0	0	0	3	0.19	1	0.06	0	0	19	3.1	0.13	2	0.13	0	0	0	0	0.5	1.0	?
64	58	37	1	0.06	0	0	2	0.13	0	0	0	0	36	2.3	0.13	2	0.13	0	0	0	0	0.5	1.0	?
68	39	27	0	0	0	0	4	0.27	0	0	0	0	49	3.3	0.14	2	0.14	0	0	0	0	2.0	1.0	?
70	61	43	0	0	0	0	1	0.07	0	0	0	0	31	2.2	0.40	7	0.40	0	0	0	0	1.0	2.0	?
72	58	42	0	0	0	0	1	0.07	2	0.14	0	0	33	2.4	0.43	6	0.43	0	0	0	0	0.5	1.0	?
75	69	52	0	0	0	0	2	0.15	0	0	0	0	22	1.6	0.52	7	0.52	0	0	0	0	0	1.0	?
75	46	34	0	0	0	0	4	0.30	2	0.15	0	0	43	3.2	0.38	5	0.38	0	0	0	0	0.5	1.0	?
76	68	52	0	0	0	0	1	0.10	0	0	0	0	24	1.8	0.30	4	0.30	0	0	0	0	0	1.5	?
77	47	36	2	0.15	0	0	0	0	0	0	0	0	44	3.4	0.54	7	0.54	0	0	0	0	1.5	5.0	?
79	62	49	0	0	0	0	1	0.32	0	0	0	0	21	1.7	0.95	12	0.95	0	0	0	0	2.0	1.0	?
79	56	44	1	0.08	0	0	0	0	0	0	0	0	30	3.1	0.32	4	0.32	0	0	0	0	1.0	2.0	?
80	61	49	0	0	0	0	0	0	0	0	0	0	34	2.7	0.40	5	0.40	0	0	0	0	1.0	4.5	?
80	54	43	0	0	0	0	5	0.40	0	0	0	0	40	3.2	0.03	1	0.03	0	0	0	0	0.2	3.0	?
88	79	70	1	0.09	0	0	0	0	0	0	0	0	17	1.5	0.26	3	0.26	0	0	0	0	0.5	3.0	?
108	61	66	0	0	0	0	10	1.08	0	0	0	0	19	2.1	1.08	10	1.08	0	0	0	0	0.5	1.0	?
Average	706	462	0.3	0.02	0.21	0.29	2.9	0.21	0.02	0.02	0.02	0.02	34.7	2.4	0.37	5.2	0.37	0.3	0.02	0.02	0.02	0.8	0.8	4.0
Maximum	108	70	2	0.15	1.08	10	10	1.08	2	0.15	0.15	0.15	58	3.5	1.08	12	1.08	6	0.41	0.41	0.41	2.0	2.0	15.0
Minimum	44	21	0	0	0	0	0	0	0	0	0	0	17	0.8	0.08	1	0.08	0	0	0	0	0	0	1.0

* See footnote, table 1

TABLE 8—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Men Twenty-Six to Thirty-Eight Years Old *

Leuko- cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
	Per Cu Mm			Per Cu Mm			Per Cu Mm			Per Cu Mm			Per Cu Mm			Per Cu Mm			Per Cu Mm			15 Min		
	%	Cu Mm	%	%	Cu Mm	%	%	Cu Mm	%	%	Cu Mm	%	%	Cu Mm	%	%	Cu Mm	%	%	Cu Mm	%	45 Min	%	45 Min
44	53	23	1	0.04	1	0.04	0	0	0	0.05	0	0	42	18	3	0.13	0	0	0	0	0	10	20	20
46	22	10	0	0	0	0	0	0	0	0.05	0	0	68	31	4	0.18	7	0.92	0	0	0	0	10	10
50	37	18	0	0	0	0.05	1	0.05	0	0	0	0	52	26	9	0.45	0	0	0	0	0	?	?	?
54	45	24	0	0	0	0	0	0	0	0	0	0	47	25	8	0.43	0	0	0	0	0	10	10	10
56	50	28	0	0	0	0.11	2	0.11	1	0.06	0	0	43	21	4	0.22	0	0	0	0	0	?	?	?
58	55	32	1	0.06	2	0.12	2	0.12	0	0	0	0	38	22	4	0.23	0	0	0	0	0	10	40	40
59	36	21	1	0.06	0	0	0	0	0	0	0	0	60	35	3	0.18	0	0	0	0	0	10	20	20
64	46	29	0	0	0	0.13	2	0.13	0	0	0	0	46	29	6	0.38	0	0	0	0	0	?	?	?
65	49	32	1	0.06	1	0.06	1	0.06	1	0.06	0	0	45	29	3	0.20	0	0	0	0	0	10	60	60
68	64	44	0	0	0	0	0	0	0	0.04	0	0	30	20	5	0.34	0	0	0	0	0	0.5	10	10
68	68	46	1	0.07	0	0	0	0	0	0.14	0	0	22	15	7	0.48	0	0	0	0	0	0.5	20	20
73	61	45	3	0.22	2	0.15	2	0.15	0	0	0	0	33	24	1	0.07	0	0	0	0	0	10	70	70
75	58	44	0	0	0	0.15	2	0.15	3	0.22	0	0	37	28	0	0	0	0	0	0	0	10	40	40
76	55	42	0	0	0	0.30	4	0.30	0	0	0	0	39	30	2	0.15	0	0	0	0	0	0.5	15	15
76	51	39	0	0	0	0.15	2	0.15	1	0.08	0	0	38	29	8	0.61	0	0	0	0	0	?	?	?
77	43	33	0	0	0	0.23	3	0.23	0	0	0	0	54	42	0	0	0	0	0	0	0	0	15	15
80	46	37	0	0	0	0.16	2	0.16	0	0	0	0	50	40	2	0.16	0	0	0	0	0	10	30	30
80	47	38	0	0	0	0.08	1	0.08	0	0	0	0	40	32	6	0.48	6	0.48	0	0	0	0	20	20
81	69	56	1	0.08	2	0.16	2	0.16	0	0	0	0	25	20	3	0.24	0	0	0	0	0	0.2	20	20
81	63	51	0	0	0	0.16	2	0.16	0	0	0	0	31	25	4	0.32	0	0	0	0	0	?	?	?
82	34	28	4	0.33	2	0.16	2	0.16	1	0.08	0	0	48	39	4	0.33	7	0.57	0	0	0	0.5	20	20
86	44	38	0	0	0	0.09	1	0.09	0	0	0	0	52	45	3	0.26	0	0	0	0	0	?	?	?
88	69	61	2	0.18	0	0	0	0	0	0	0	0	29	26	2	0.18	0	0	0	0	0	10	25	25
96	44	42	4	0.38	3	0.29	3	0.29	1	0.10	0	0	46	44	2	0.19	0	0	0	0	0	10	10	10
100	75	75	0	0	0	0.20	2	0.20	0	0	0	0	23	23	0	0	0	0	0	0	0	0.5	10	10
100	55	55	0	0	0	0.20	2	0.20	0	0	0	0	59	39	1	0.40	0	0	0	0	0	?	?	?
104	51	53	0	0	0	0.21	2	0.21	1	0.10	0	0	45	47	1	0.10	0	0	0	0	0	10	50	50
108	66	71	0	0	0	0.11	1	0.11	0	0	0	0	25	30	3	0.32	0	0	0	0	0	0.5	20	20
Average	748	398	0.7	0.06	1.5	0.11	0.5	0.63	0.5	0.63	0.63	0.63	41.1	29.9	3.6	0.25	0.7	0.05	0.7	0.05	0.7	0.7	2.6	2.6
Maximum	108	75	4	0.38	4	0.30	3	0.22	3	0.22	0.22	0.22	68	47	9	0.61	7	0.57	7	0.57	7	10	70	70
Minimum	44	23	0	0	0	0	0	0	0	0	0	0	22	15	0	0	0	0	0	0	0	0	10	10

* See footnote, table 1

TABLE 9—Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Women Twenty-Three to Thirty-Six Years Old and of Men and Women Twenty-Three Years of Age and Over *

Leuko- cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Lymphocytes			Monocytes			Dis-integrated Cells			Sedimentation Rate		
	Per Mm			Per Mm			Per Mm			Per Mm			Per Mm			15 Min		
	%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	%	Cu	Mm	%	15 Min	15 Min
Women																		
16	42	19	0.09	0	0	0.05	55	25	0	0	0	0	0	0	0	90	290	0
18	56	27	0	0	0	0.06	41	20	0	0.11	0	0	0	0	0	70	250	0
55	12	23	0	0	0.12	0	41	23	0	0.50	0	0.8	0	0	0	10	10	10
58	59	31	0.06	1	0.06	0	30	17	0	0.41	0	0	0	0	0	0.5	15	15
59	52	11	0.06	1	0.06	0	43	17	0	0.18	0	0	0	0	0	?	?	?
60	72	13	0.12	2	0.12	0	20	12	0	0.21	0	0	0	0	0	0.5	10	10
62	72	22	0	1	0.25	0	35	22	0	0.70	0	0	0	0	0	20	180	0
62	35	22	0.06	0	0	0	61	38	0	0.06	0	0	0	0	0	10	60	0
63	71	17	0	0	0.13	0	25	11	0	0.06	0	0	0	0	0	15	85	0
65	51	33	0.21	1	0.13	0	38	25	0	0.52	0	0	0	0	0	10	120	0
70	53	37	0.07	2	0.07	0	35	27	0	0.28	0	0	0	0	0	?	?	?
71	53	38	0.07	1	0.14	0	37	26	0	0.60	0	0	0	0	0	20	80	0
73	59	13	0.07	1	0.07	0	32	23	0	0.51	0	0	0	0	0	10	80	0
74	67	50	0	0	0	0.07	26	19	0	0.11	0	0	0	0	0	10	50	0
78	54	42	0	1	0.23	0	37	29	0	0.40	0	0	0	0	0	15	110	0
80	62	50	0	1	0.08	0	32	26	0	0.16	0	0	0	0	0	?	?	?
82	59	66	0	0	0	0.08	17	11	0	0.35	0	0	0	0	0	20	150	0
88	80	52	0	1	0.09	0	36	32	0	0.35	0	0	0	0	0	0.5	20	0
89	62	55	0.18	2	0.18	0	31	28	0	0.27	0	0	0	0	0	30	20	0
90	49	44	0.09	1	0.18	0	44	40	0	0.27	0	0	0	0	0	10	20	0
100	51	56	0	0	0.11	0	41	15	0	0.11	0	0	0	0	0	20	80	0
118	91	99	0	0	0	0	6	07	0	0	0	0	0	0	0	0.5	70	0
Average	78.1	129	0.05	1.1	0.08	0.6	34.7	24.4	1.2	0.29	0.6	0.07	0.6	0.07	0.07	1.9	10.5	10.5
Maximum	91	99	0.21	1	0.25	3	61	45	9	0.52	7	0.65	7	0.65	0.65	90	290	0
Minimum	35	19	0	0	0	0	6	07	0	0	0	0	0	0	0	0.5	10	10
Men and Women																		
744	73.9	107	0.04	2.2	0.17	0.4	38.3	2.8	1.2	0.30	0.5	0.03	0.5	0.03	0.03	0.8	15	15
727	73.1	129	0.05	1.1	0.08	0.6	31.7	2.44	1.2	0.29	0.6	0.03	0.6	0.03	0.03	1.9	10.5	10.5
Average	74	111	0.04	2	0.16	0.5	37.6	2.73	1.2	0.30	0.5	0.03	0.5	0.03	0.03	1.0	17	17
Maximum	91	99	0.08	10	1.08	3	68	49	12	1.36	10	0.65	10	0.65	0.65	90	290	0
Minimum	22	10	0	0	0	0	6	07	0	0	0	0	0	0	0	0	10	10

* See footnote, table 1

TABLE 10—Summary of Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Adults Nineteen Years of Age and Over †

Age	Cases	Leuko cytes per Cu Mm	Neutrophil Lobocytes			Neutrophil Rhabdocytes			Eosinophil Lobocytes			Basophil Lobocytes			Lymphocytes			Monocytes			Disintegrated Cells			Sedimentation Rate		
			Per		%	Per		%	Per		%	Per		%	Per		%	Per		%	Per		Cu Mm	15 Mm	45 Mm	
			Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm		Cu	Mm				Cu
19	16	7 22	47 9	3 46	0 5	0 03	1 4	0 10	0 6	0 04	42 8	3 09	1 8	0 35	1 9	0 13	0 6	2 2								
20	17	7 01	35 9	3 30	0 5	0 03	2 0	0 14	0 2	0 01	36 7	2 39	4 2	0 30	0 4	0 02	0 9†	5 3†								
21	39	6 91	51 5	3 60	0 9	0 07	1 8	0 13	0 7	0 05	40 1	2 73	3 8	0 27	1 0	0 06	0 7†	2 6†								
22	33	7 60	54 2	4 16	0 5	0 03	1 3	0 13	0 4	0 03	33 1	2 86	4 3	0 33	0 6	0 04	1 68	5 78								
23	26	7 49	54 1	4 10	0 5	0 03	2 7	0 21	0 4	0 03	37 4	2 79	4 0	0 30	0 8	0 04	0 8	3 1								
24	17	7 76	53 6	4 22	0 4	0 03	1 8	0 15	0 5	0 03	39 7	3 01	3 9	0 31	0	0	0 8	1 8								
25	22	7 06	56 2	4 02	0 3	0 02	2 9	0 21	0 3	0 02	34 7	2 40	5 2	0 7	0 3	0 02	0 8#	4 6#								
26-38	23	7 48	52 0	3 98	0 7	0 06	1 5	0 11	0 5	0 03	41 1	3 00	3 6	0 25	0 7	0 05	0 7**	2 6**								
Average	198	7 30	53 2	3 92	0 6	0 04	2 0	0 15	0 5	0 03	38 8	2 80	1 2	0 31	0 7	0 05	0 9††	3 7††								
Maximum		12 40	79 0	9 0	7 0	0 85	10 0	0 98	4	0 34	68	4 9	12	1 36	11	0 68	13 0	46 0								
Minimum		4 40	22 0	1 0	0	0	0	0	0	0	16	0 8	0	0	0	0	0	0								
Men																										
Women																										
19	17	7 53	54 1	4 15	0 6	0 04	1 1	0 09	0 5	0 03	33 5	2 80	3 9	0 31	1 2	0 10	1 8	11 2								
20	13	7 95	51 7	4 11	1 3	0 10	2 8	0 21	0 4	0 03	39 5	3 18	4 1	0 30	0	0	1 8	13 7								
21	10	7 65	59 0	4 65	2 7	0 20	1 2	0 10	0 5	0 03	31 5	2 29	3 1	0 24	2 0	0 16	1 8	11 3								
22	9	6 93	55 8	3 90	1 1	0 08	1 4	0 10	0 2	0 02	34 7	2 36	6 1	0 43	0 7	0 05	2 7	11 8								
23-36	22	7 27	53 1	4 29	0 7	0 05	1 1	0 08	0 6	0 01	34 7	2 44	4 2	0 29	0 6	0 05	1 9	10 5								
Average	71	7 47	55 8	4 22	1 1	0 03	1 5	0 11	0 5	0 03	36 0	2 63	4 2	0 31	0 8	0 06	2 0	11 6								
Maximum		13 2	94	11 0	8	0 74	9	0 69	3	0 27	61	6 5	11	1 04	14	1 09	9 0	35 0								
Minimum		4 6	29	1 9	0	0	0	0	0	0	6	0 7	0	0	0	0	0	1 0								
Men and Women																										
198	7 30	53 2	3 92	0 6	0 04	0 15	2 0	0 15	0 5	0 03	38 8	2 80	4 2	0 31	0 7	0 05	0 9††	3 7††								
71	7 47	55 8	4 22	1 1	0 03	0 11	1 5	0 11	0 5	0 03	36 0	2 63	1 2	0 31	0 8	0 06	2 0	11 6								
269	7 35	53 9	4 01	0 7	0 03	0 14	1 8	0 14	0 5	0 03	38 1	2 76	1 2	0 31	0 7	0 05	1 2††	5 9††								
Average		13 2	94	11 0	8	0 85	10	0 98	4	0 34	68	4 5	12	1 36	14	1 09	13 0	46 0								
Maximum		4 4	22	1 0	0	0	0	0	0	0	6	0 7	0	0	0	0	0	0								
Minimum																										

* See footnote, table 1
† Fifteen cases
‡ Thirty six cases
§ Thirty cases
|| Twenty five cases
¶ Thirteen cases
Twenty cases
** Twenty one cases
†† One hundred and seventy six cases
‡‡ Two hundred and forty seven cases

In making the differential counts, 200 or more cells were classified according to the criteria described and illustrated in the "Atlas of Hematology,"¹² care being taken to study only portions of the smears so thin that the akaryocytes (erythrocytes) were not touching each other. The absolute leukocyte counts were calculated by multiplying the total leukocyte count by the percentage of the particular cell type. Plum¹³ gave data from which the probable error of any of these determinations may be calculated.

The sedimentation rates were determined¹⁴ on the same samples of oxalated blood, a Westergren pipet being used and readings being taken after fifteen and forty-five minutes. Experience with over 80,000 determinations by this method has shown it to have the advantages of the graphic methods and to be simpler and quicker.

TABLE 11—*Statistical and Smoothed Means and Ranges for Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Adults Nineteen Years of Age and Over*

		Statistical Mean	Probable Error Distribution	Smoothed Mean	95% Range
Leukocytes*	Per cu mm	7,410 \pm 70	1,145 \pm 23	7,400	4,000-11,000
Neutrophil†	%	54.3 \pm 0.5	7.1 \pm 0.2†	54	33-75
lymphocytes	Per cu mm	4,085 \pm 66	Skew	4,000‡	1,500-7,500§
Neutrophil	%			1*†	0.5*†
rhabdocytes†	Per cu mm			50	0-200*†
Eosinophil	%			2*†	0.6*†
lymphocytes†	Per cu mm			150*†	0-400*†
Basophil	%			0.5†	0.2†
lymphocytes†	Per cu mm			50†	0-200†
Lymphocytes†	%	37.7 \pm 0.5	7.6 \pm 0.2	38	15-60
	Per cu mm	2,782 \pm 39	Skew	2,750	1,000-4,500
Monocytes†	%			4*†	0.9*†
	Per cu mm			300†	0-500†
Disintegrated	%			3*†	0.7†
cells†	Per cu mm			250*†	0-600*†
Sedimentation	15 min	Skew		2.0†	0.5-5.0†
rate	45 min	Skew		10.0†	1.0-30.0†

* Applies to persons 19 years of age and over

† Applies to persons 20 years of age and over

‡ Applies to persons 8 to 14 years of age

§ Applies to persons 4 to 7 and 15 years of age and over

|| Applies to persons 15 years of age and over

¶ Applies to persons 4 years of age and over

RESULTS

Tables 1 to 9 summarize the individual results for the total, differential and absolute leukocyte counts and sedimentation rates for each age and sex group. On examination of these tables and the scatter diagrams^{1d} it is evident that there is no significant difference with age or sex within this group, so that it is justifiable to summarize the results for the entire group, as has been done in table 10. This table gives the averages and extreme ranges. For clinical purposes, however, the

13 Plum, P. Accuracy of Haematological Counting Methods, Acta med Scandinav 90 342-364, 1936

14 Osgood,¹⁰ p 430

most useful range of normal values is not the extreme range but that which will include about plus or minus three probable errors, or 95 per cent of healthy persons. In other words, if a result in a person of this age group falls outside of this range there is less than one chance in twenty that it is normal for that person. These 95 per cent ranges are summarized in table 11.

COMMENT

The proportion of lymphocytes is higher and of neutrophil lobocytes (polymorphonuclears) lower than the textbook figures. The probable explanation for the retention of erroneous figures in the textbooks is that these figures represent fairly closely the usual counts of patients sick enough to be attending an outpatient clinic or to be hospitalized but who are not suffering from a generally recognized cause of marked leukocytosis. The dangers of using such persons as normal subjects are obvious.

In this age group the leukocyte count is lower, the neutrophil percentage is higher and the lymphocyte percentage is lower than the corresponding figures for younger persons.¹ It is of interest that the absolute number of neutrophil lobocytes (polymorphonuclears) averages 4,000 per cubic millimeter for all ages from 4 to 30 years except for the age group 8 to 14 years.

The sedimentation rates form a skew curve, with the greatest number of determinations falling in the lower ranges. It is probable that the rate of 15 mm in forty-five minutes, which includes 80 per cent of the results, represents the strict upper limit of normal values and that the higher rates are due to mild chronic infection in the tonsils, teeth or sinuses not detectable in the routine physical examination.

SUMMARY

There are no significant age or sex differences in the total, differential or absolute leukocyte counts or in the sedimentation rates in persons 19 to 30 years of age. Table 11 gives the data which should be most useful in interpretation of each of these determinations in persons of this age group. These results agree well with those reported by Galambos in 1912 but differ from the figures given in most textbooks.

LIMITATIONS OF BIOPSY OF STERNAL MARROW

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In recent years clinical hematologists have devoted considerable attention to the cytologic structure of bone marrow removed at biopsy. Published accounts of their experience vary greatly in enthusiasm and in detail. Sufficient controversy surrounds the entire subject to justify a report of our experience at the University of Chicago Clinics and in the "Medicine A" service of St. Luke's Hospital. No attempt will be made to review or summarize the entire literature, and the papers referred to are those that amplify, controvert or illustrate our own opinions.

Marrow for study has been obtained chiefly from the tibia and the sternum, the latter source was most frequently chosen. Peabody¹ and Nordenson,² as well as others, have shown that the functioning marrow removed from different bones tends to be similar. In fact, the prime justification for selecting any single region from which to take biopsy material is the assumption that it is representative of the hemopoietic system as a whole. Two techniques for obtaining marrow are commonly used. One requires the removal of a button of bone with its underlying marrow by means of a trephine. Usually more marrow is curetted out with a spoon. The button is fixed and decalcified, and sections are cut and stained. The curetted material may be similarly treated, although usually smears or "touch" preparations are made from it. Interpretation of fixed tissue is somewhat more difficult for the hematologist, because the cells do not look quite like their counterparts in the conventional films of peripheral blood stained with Wright's stain or a related stain. On the other hand, cellular relations are maintained, and an estimate of the cellularity of the tissue is easy and more accurate. The entire

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1 Peabody, F. The Pathology of the Bone Marrow in Pernicious Anemia. *Am J Path* **3** 179, 1927, A Study of the Hyperplasia of the Bone Marrow in Man, *ibid* **2** 487, 1926

2 Nordenson, N. G. Histologic Quantitative Studies of Normal and Pathologic Bone Marrow. *Hygica* **96** 193, 1934

surgical procedure should cause no discomfort. It ought, however, to be performed under strictly aseptic conditions, as in a regular operating room.

Removal of biopsy material by means of a needle or a trocar is easier, can be done with less apparatus and need not be performed in an operating room, although an aseptic technic should be followed. Our practice is to use a shortened 14 gage spinal puncture needle with a firm finger grip and a stilet. After inducing regional anesthesia with a 2 per cent solution of procaine hydrochloride, we introduce the needle directly through the outer lamina of the manubrium or body of the sternum. We can see no advantage in entering the marrow cavity through the articulations. The material to be studied is aspirated by gentle suction with a small syringe, and as small an amount of marrow as possible is removed. We stop suction when blood appears in the syringe, the contents of the needle and its hub amount to from 0.1 to 0.2 cc. The aspirated material may be placed in an oxalated or heparinized tube, cell counts and smears being made at one's leisure. The total cell counts are so variable, depending as they do on dilution with circulating blood when larger volumes of marrow contents are aspirated, that we have stopped doing them. (Segerdahl³ has shown that in normal persons the standard deviation of the total white cell count is from 40 to 50 per cent of the mean, hence few counts will be significant.) We make direct smears of the material on slides before it coagulates and rely on our judgment for an estimation of the cellularity. Fat droplets are easily seen, and their presence or absence influences considerably our interpretation of the state of the marrow. Our smears are stained with Wright's stain or May-Grunwald-Giemsa stain.

The marrow having been acquired and stained, the difficulty of interpretation arises. It is our custom to designate the cells according to the terminology of Downey. The smears should be studied generally at first, notice being taken of the cellularity, the amount of fat, the predominant cell types and the presence of definitely abnormal cells or parasites, if any. A crude estimate may be made of the ratio of white cells to nucleated red cells. In general, this survey supplies one with the most information. After this it is our custom to perform a differential count of 500 to 1000 cells, using several portions of several smears. Neither of these phases of the examination should be done by laboratory technicians, but if the clinician is too busy to perform a differential count at least he should study the slide with considerable care. The chief value of the differential count is to confirm one's impression about predominating cell types and to establish the leukocyte-

³ Segerdahl, E. Ueber Sternalpunktionen, *Acta med Scandinav*, 1935, supp 64, p. 1.

erythrocyte ratio. Comparison of the differential counts with any of several tables of normal values at once brings out the confusing fact that the normal is variable. In table 1 are listed four such standards. We have translated (correctly, we hope) differing nomenclatures into the one we adhere to. We wish to call attention particularly to the normal values listed by Segerdahl, whose work is not widely enough known. She treated her extensive data on normal values statistically, and in the second column of her figures is given the standard deviation. She demonstrated that unless the actually observed number of any cell series is greater than her mean plus three times the standard deviation or less than the mean minus three times the standard deviation it cannot be

TABLE 1—Normal Values According to Several Observers*

Cell Type	Segerdahl†		Arinkin, Average	Young and Osgood, Average	Vogel, Erf and Rosenthal, Average
	Mean	Standard Deviation			
Myeloblasts	1.32	0.77	1.7	0.4	1.6
Promyelocytes	1.35	0.76	1.9	1.2	21.5
Neutrophilic myelocytes	15.0	3.76	6.55	0.8	
Eosinophilic myelocytes	1.37	0.63	0.65		0.7
Neutrophilic metamyelocytes	15.69	3.22	2.4	1.8	0.2
Neutrophilic stab/band forms	10.48	3.73		25.0	
Neutrophilic polymorphonuclears	20.86	5.47	48.0	13.3	34.0
Eosinophilic polymorphonuclears	1.44	0.77	2.3	0.4	0.9
Basophilic polymorphonuclears	0.14	0.12	0.35	0.1	0.7
Monocytes	1.67	0.62	5.7	2.1	
Lymphocytes	16.76	4.77	11.9	10.6	8.6
Frythroblastic series (all nucleated red cells)	12.88	4.79	12.7	14.1	29.84
Histiocytes	0.03	0.07	‡	‡	0.3
Megakaryocytes	0.03	0.05	3.35		0.2
Plasma cells	0.39	0.35	0.6		

* Segerdahl,† Arinkin, A. Die intravitale Untersuchungsmethodik des Knochenmarks, *Poln. haemat.* 35, 233, 1929. Young, R. H., and Osgood, E. E. Sternal Marrow Aspirated During Life. *Cytology in Health and in Disease*, Arch. Int. Med. 55, 186 (Feb.) 1935. Vogel, P., Lrf, L. A., and Rosenthal, N. Hematological Observations on Bone Marrow Obtained by Sternal Puncture, *Am. J. Clin. Path.* 7, 436 and 495, 1937.

† Segerdahl's data are based on a group of 52 men.

‡ Included with the monocytes.

considered significantly abnormal. Particular attention is called to the large size of the standard deviation. Segerdahl's figures carry weight because of the large number of biopsies of normal tissue that supplied them. It may be stated that her experience with normal values is closely paralleled by our own.

The great variability of the normal, whether expressed as the standard deviation or as the range, makes it impossible to place any reliance on subtle changes in the constitution of the marrow as seen in preparations obtained by sternal puncture. In addition to the changeability expressed so impersonally by statistical methods, two other sources of variation are seen. One is the conspicuous difference in cellularity of the several slides made. In too thick preparations only the peripheral portions stain well enough for easy identification. One also frequently sees large

aggregates of marrow cells which may be discrete enough for counting. These clumps generally yield differential counts at variance with the counts obtained from more homogeneous areas. Although accurate counting of such groups is difficult, we have reason to believe that such masses are more truly representative of the actual state of the marrow, and we seek them out. The other source of variation in results is the unconscious and purely arbitrary selection of certain regions of the several slides for counting. It was curious but not surprising to find, when we reexamined our material and recounted the cells in preparing this paper, how great was the discrepancy. Frequently four differential counts were recorded, all considerably different, and although they were

TABLE 2—Results of Four Differential Counts of Sternal Marrow

Cell Type	Counter			
	E V K	G V L	E V K	G V L
Myeloblasts	15	08	08	10
Promyelocytes	35	02	0	10
Neutrophilic myelocytes	45	82	36	100
Neutrophilic metamyelocytes	380	258	225	177
Neutrophilic band forms	320	125	118	226
Neutrophilic polymorphonuclears	405	262	502	389
Eosinophils, all types	0	02	06	20
Basophils	0	0	0	05
Lymphocytes	10	08	06	0
Monocytes	0	0	0	23
Basophilic erythroblasts	}	10	04	05
Polychromatic erythroblasts		}	92	31
Orthochromatic erythroblasts				10

* These counts were performed by each of us on the same material. Examination of the peripheral blood of the subject on the day biopsy was performed revealed the following values: hemoglobin, 10.9 Gm.; red blood cells, 3,900,000 per cubic millimeter, and white blood cells, 22,200 per cubic millimeter. The differential count showed 89.5 per cent polymorphonuclears, 7 per cent lymphocytes and 3.5 per cent monocytes.

not mutually exclusive for diagnostic purposes, this discrepancy has caused us to look with some suspicion on reports of workers who recognize subtle diagnostic patterns in their differential counts of sternal marrow. In table 2 is presented an example of our experience in this respect. The patient had recently recovered from lobar pneumonia, but a high leukocyte count persisted for no obvious reason. The marrow was considered normal, and in several months the leukocyte count returned to normal levels.

If considered alone—that is, without the other clinical data—and frequently even with it, the results of biopsy of sternal marrow can be misleading. Brief abstracts of illustrative cases are presented, and the differential counts for the sternal marrow and the peripheral blood for the same day are listed in table 3.

REPORT OF CASES

CASE 1—A 54 year old man had severe unexplained anemia. There were generalized enlargement of the lymph nodes and moderate hypertrophy of the liver and spleen. Two biopsies of material from the lymph nodes disclosed only simple hyperplasia. After the repair of a rectal prolapse and administration of copious doses of an iron compound the anemia gradually improved, and the patient stopped coming to the clinic.

CASE 2—A 59 year old man was known to have had Hodgkin's disease of nineteen years' duration. The differential count of the peripheral blood was typical of this disease. Epidural infiltration of the sacral and lumbar roots had caused paraplegia. There was no other apparent skeletal involvement.

TABLE 3—*Differential Counts of Peripheral Blood and Sternal Marrow* in Cases 1 to 5*

	Case 1		Case 2		Case 3		Case 4		Case 5	
Peripheral blood on day of biopsy										
Hemoglobin, Gm per 100 cc	6.0		14.0		12.4		12.6		15.1	
Red blood cells	1,890,000		4,000,000		4,670,000		3,730,000		3,540,000	
White blood cells	6,000		7,200		9,250		16,000		14,900	
Polymorphonuclears	90		88		60		32		35	
Lymphocytes	7		10		39		67		62	
Monocytes	2		2		1		1		1	
Eosinophils	1								2	
Basophils										
Sternal marrow										
Myeloblasts	0.7	0.6	1.0	0	0	0.2	3.0	2.0	0.3	0.7
Promyelocytes	1.1	2.0	2.8	1.1	0	0.9	0.4	0.7	0.6	0.4
Myelocytes	6.0	9.1	12.1	10.9	3.3	2.1	5.0	5.0	3.3	3.1
Metamyelocytes	18.3	11.0	12.0	16.7	2.3	9.0	10.2	8.1	12.1	6.6
Band forms	16.6	23.5	34.2	23.5	25.6	32.1	20.0	25.9	4.6	11.7
Polymorphonuclears	14.2	6.5	16.7	13.7	40.3	18.2	7.0	10.0	19.0	18.3
Eosinophils (all types)	1.1	2.5	4.0	4.8	5.3	7.3	0	0.7	4.0	1.8
Basophils	0.2	0.1	0	0	0	0.2	0.2	0.2	0.2	0.4
Lymphocytes	3.1	10.0	4.5	4.5	5.0	7.9	24.0	20.2	10.6	34.5
Monocytes	0	1.1	1.4	0.6	0	2.1	0	0.5	0.6	2.5
Histiocytes	0.9	3.1	0	0.4	0	0	1.0	0.5	0.3	0
Megakaryocytes	0.4	0.1	0.5	0.4	0	0.2	0	0	0	0
Basophil erythroblasts	17.1	16.5	2.0	1.4	0.3	1.3	3.2	1.6	0	1.8
Polychromatic and orthochromatic erythroblasts	15.3	10.0	18.2	17.1	17.6	14.8	26.0	25.8	28.0	16.3

* The differential counts of cells in the sternal marrow are given in duplicate to emphasize the personal variation. The counts in the left hand column in each case are by L V K.

CASE 3—A 67 year old man was known, on the basis of biopsies of tissue from the lymph nodes, to have had lymphosarcoma for seven years. At the time of the sternal puncture he had copious ascites and hydrothorax. The fluid removed by paracentesis was creamy owing to the large number of small lymphocytes that it contained.

CASE 4—A 57 year old man had suffered with chronic lymphatic leukemia for five years. There was never any suspicion of osseous involvement. The patient died, and autopsy disclosed little heteroplasia of the marrow.

CASE 5—A 69 year old man suffered from angina pectoris. He had moderate hyperchromic macrocytic anemia, associated with achlorhydria after stimulation with histamine. The condition was unresponsive to liver therapy. The lymphocytosis and the anemia persisted until the patient ceased to attend the clinic. The condition was never explained.

The finding of apparently normal marrow in these patients may be interpreted in various ways. In cases 1 and 5 the entire disease process was obscure, and although one might expect the marrow to be abnormal, it is unjustifiable to say that the specimens studied were not representative. In case 2, in which there certainly must have been skeletal involvement, chance must have supplied us with normal-appearing marrow. In the other 2 cases it is reasonable to think that the lymphomatous process simply had not extended to the portions of the marrow studied.

Similar in some respects to the first 5 patients were 6 additional patients with definite disturbances of the hemopoietic system. The

TABLE 4—*Differential Counts of Peripheral Blood and Sternal Marrow* in Cases 6 to 11*

	Case 6		Case 7		Case 8		Case 9		Case 10		Case 11					
Peripheral blood on day of biopsy																
Hemoglobin, Gm per 100 cc	13.9		14.2		14.2		14.6		7.0		7.7					
Red blood cells	3,970,000		4,560,000		4,250,000		4,400,000		2,900,000		2,030,000					
White blood cells	2,200		2,400		4,700		3,000		6,800		5,920					
Polymorphonuclears	53		70		65		57		67		22					
Lymphocytes	42		25		24		40		26		75					
Monocytes	3		4		7		3		6		3					
Eosinophils	1		1		2				1							
Basophils					1											
Sternal marrow																
Myeloblasts	3.0	2.0	1.8	0.4	0	0.8	1.4	†	1.5	2.8	1.0	0				
Promyelocytes	2.5	0.8	2.0	1.9		1.6	3.2	1.0	1.7	0	3.0	0.4				
Myelocytes	7.2	5.2	14.2	10.4		9.4	6.1	6.0	0.8	2.8	3.5	5.2				
Metamyelocytes	8.0	7.5	8.0	9.3		6.5	10.0	10.0	7.4	7.6	7.5	4.3				
Band forms	16.0	22.5	16.6	22.9		29.0	14.1	20.8	24.1	10.0	19.0	18.1				
Polymorphonuclears	6.0	6.5	17.0	14.1		9.0	15.8	6.0	13.3	27.3	5.0	6.9				
Eosinophils (all types)	3.2	7.5	0	0.9		2.5	4.2	1.2	1.4	3.0	7.0	5.2				
Basophils	0	0.5	0	0.4		0.2	0.3	0	0.2	0	0	0				
Lymphocytes	7.0	4.2	7.0	5.1		5.7	11.2	11.6	10.6	1.0	17.5	19.3				
Monocytes	1.2	0.3	2.2	1.3		1.0	1.2	2.0	0.4	0	0	2.2				
Basophilic erythrocytes	4.2	0.6	5.0	2.3		1.8	1.6	2.5	14.6 39.0 {							
Polychrome and ortho- chrome erythrocytes	51.0	41.9	21.2	29.1		30.6	40.4	37.1					{		2.3 31.9	
Megakaryocytes	0	0	0	0.2		0	0.3	0.9								

* The differential counts for the sternal marrow are given in duplicate as in table 3.

† This biopsy was performed just one year after the one recorded to the left.

condition of 5 of these was tentatively diagnosed as Banti's syndrome. By this we mean nonspecific fibrosis of the spleen and liver associated with refractory anemia and leukopenia and with varying evidence of hypertension in the portal vein. It is strange that such a disturbance of hemopoiesis as was indicated by the peripheral blood of these patients should be associated with no significant morphologic changes in the marrow. The differential counts for the marrow and blood of this group are given in table 4.

CASE 6—A 40 year old woman was referred to the clinic because of considerable enlargement of the liver and spleen and because of leukopenia which defied therapy. She had moderate ascites, and esophageal varicosities were seen on fluoroscopic examination. Splenectomy was attempted but could not be com-

pleted because of dense adhesions. Biopsy of tissue from the liver revealed considerable portal fibrosis. The patient remained well, although the abnormality of the blood persisted.

CASE 7—A 28 year old woman was found to have moderate hepatosplenomegaly and leukopenia. Esophageal varices were seen by the roentgenologist. Splenectomy was recommended, but the patient declined and did not return to the clinic.

CASE 8—A 30 year old woman consulted us because of an enlarged liver. She had only moderate leukopenia, no anemia, no esophageal varices and no demonstrable ascites. There were definitely dilated veins over the lower part of the abdomen, suggestive caput medusae. A successful splenectomy was performed. The histologic diagnosis was splenic fibrosis of the type associated with Banti's syndrome. After the operation the liver increased in size, but the patient remained well.

CASE 9—A 49 year old woman was first seen by us because of a purpuric tendency. There was no abnormality of the coagulation mechanism as far as we could determine. The patient had a large spleen, an enlarged liver and persistent leukopenia. There was persistent occult blood in the stools from no recognizable point. During frequent roentgen examinations for the source of bleeding, extremely large esophageal varices were discovered. An exploratory operation was performed in the hope of removing the spleen as well as being able thoroughly to examine the gastrointestinal tract. For technical reasons the spleen could not be removed. After the exploratory procedure the patient was well, and, strangely, when she felt ill a small dose of roentgen therapy to the spleen cured her. The second biopsy of sternal marrow was performed a year after the first. The blood picture was essentially unchanged.

CASE 10—A 36 year old man was seen by us after a severe gastrointestinal hemorrhage. Moderate enlargement of the spleen was the sole physical abnormality. Thorough fluoroscopic examination failed to disclose the source of the hemorrhage and revealed no esophageal varices. Surgical exploration disclosed a few large veins around the duodenum and a greatly enlarged splenic vein. It was assumed that the condition was Banti's syndrome in the early stages. After the operation there was persistent occult blood in the stools, but no more gross hemorrhages occurred and the patient felt well.

CASE 11—A 38 year old man with severe jaundice, low grade fever, hepatosplenomegaly and malleolar ulceration, all due to syphilis, was seen by us because of persistent anemia. Eventually, with appropriate antisyphilitic treatment, he became completely well, the spleen and the liver returning to apparently normal size.

These 6 cases had several features in common, particularly splenomegaly, anemia and leukopenia. Biopsy of marrow displayed in each a rather large, but not significantly large, percentage of nucleated red cells. This may have been due in part to the tendency to hemorrhage from which all of the patients suffered more or less. It is curious that in case 11, the only one in which the cause of the pathologic process was known, the marrow was so similar to that observed in the others. The only benefit derived from these biopsies was the assurance that the

splenomegaly and the disturbance in the blood picture were not part of a leukemic process, and we were already certain of this

We have mentioned that the rather high percentage of nucleated red cells in the marrow of the 6 patients just described may have been due to chronic loss of blood. This may be true, but we are able to produce from our records several instances in which it has not been true of patients with severe anemia due to loss of blood or to indefinite toxic states. The counts performed on the blood and marrow of 4 such patients are contained in table 5, and brief abstracts of the case records follow

CASE 12—A 22 year old man underwent a radical operation on the antrum for severe chronic sinusitis. Ten days later he had a massive hemorrhage from the nose, and the hemoglobin value fell to 7.2 Gm per hundred cubic centimeters of blood. Sternal marrow was taken for biopsy six days later, after two transfusions and oral administration of an iron compound had raised the hemoglobin content to 12.4 Gm per hundred cubic centimeters.

CASE 13—A 73 year old man was admitted to the hospital because of severe diarrhea, intestinal cramps and loss of weight. A leukemoid reaction was noted in the blood. He failed rapidly and died. Autopsy disclosed severe ulcerative colitis, hemorrhage from which was the apparent cause of the anemia.

CASE 14—A 35 year old man came to us because of severe intractable anemia. There was no external bleeding, but the stools contained much occult blood. The platelets numbered 90,000. The bleeding time was two hours and the coagulation time three minutes, but the clot did not retract. On the basis of a diagnosis of idiopathic thrombocytopenic purpura splenectomy was performed. The operation was successful. The patient recovered in a spectacular manner and was still well a year later.

CASE 15—A 58 year old woman was admitted to the ward at St. Luke's Hospital with severe anemia and leukopenia. The platelet count was 20,000. The bleeding time was prolonged, the clotting time was normal, but the clot failed to retract. The patient stated that she had had frequent epistaxis, and with case 14 in mind a diagnosis of thrombocytopenic purpura plus leukopenia was made and splenectomy was recommended. The patient refused the operation, and medical treatment with transfusions, an iron compound, ascorbic acid and yellow bone marrow was instituted. The anemia improved, but it promptly relapsed when these medicaments were stopped. Finally, two courses of roentgen therapy to the spleen were tried. The platelets increased to 350,000 and the white cells to 7,200. The permanence of the remission was not certain.

Inspection of the biopsy specimen and determination of the number of cells in the 4 preceding cases gave little evidence as to the nature of the underlying pathologic process. A diminution of platelets was noted in cases 14 and 15, but little else. As we have mentioned, for these patients biopsy served a good purpose in a clinical sense, for it suggested to us that the severe anemia did not have as a background some severe myelopathy, such as aplastic anemia or atypical leukemia. However, we

were reasonably sure of the diagnosis before the biopsy was performed, and the chief reason for performing it was to illuminate, if possible, the pathologic process under observation. Nevertheless, it was encouraging to have such added assurance. Other, less spectacular instances in which the negative findings at biopsy were of use to us are also included in table 5.

CASE 16—A 16 year old boy was brought to us by his mother because he looked ill. A brother had died the year before of acute myeloid leukemia, and the mother was terrified lest a similar disease should affect the present patient. Physical examination showed normal conditions in every respect, as did hematologic investigation.

CASE 17—A 34 year old man was studied because of persistent leukocytosis, the white blood cell count ranging from 15,000 to 20,000. The condition was unaccompanied by fever. There was slight diarrhea, for which no cause was found. Biopsy of sternal marrow eliminated a persistent suspicion that incipient leukemia was responsible for the high white cell count. Subsequently the diarrhea became more severe, and finally terminal ileitis was diagnosed. Appropriate treatment of this condition was followed by a return of the white cell count to normal.

CASE 18—A 44 year old man presented himself to the diagnostic clinic at St Luke's Hospital, complaining of headaches. A roentgenogram of the skull disclosed spectacular round, oval and multiloculated regions of increased radiolucency, and multiple myeloma was justifiably suspected. After all the studies were completed the patient recalled that three years earlier a similar diagnosis had been made and he had been told that he had only a few years to live. Comparison of the films showed absolutely no change, and the abnormal areas were considered to be venous lakes or developmental anomalies.

CASE 19—A 36 year old man was referred to one of us by Dr. C. E. Shannon, of Chicago. He had a peculiar deforming lesion of the right femur, with increasing coxa vara. Roentgenographically the medullary cavity displayed coarse secondary trabeculae, evidence of bone absorption and some cystlike areas. Diagnostic guesses varied, localized osteitis fibrosa cystica, atypical Paget's disease and atypical Gaucher's disease were suggested. The normal sternal marrow was of interest, and precise chemical studies suggested a diagnosis of hyperparathyroidism.

CASE 20—A 31 year old man who had been doing field work in archeology in Asia Minor came to the clinic because he "felt like his malaria was returning." Careful study of the sternal marrow revealed no Plasmodia, and the patient, satisfied, had no more peculiar feelings.

Although the majority of biopsies of sternal marrow reveal nothing or are at most of academic interest (as when the diagnosis is already sufficiently obvious from other clinical studies), there are occasions when the material from the marrow cavity is helpful. Such occasions occur when definitely abnormal cells are encountered. These may be evidence of metastases or of heteroplasia or there may be parasites, but the demonstration of them is significant. Frequently they cannot be identified, but the mere finding of them may illuminate an otherwise

obscure situation There have also been a few times when we were confronted with peculiar clinical syndromes in which the differential count of the sternal marrow was definitely diagnostic Table 6 contains the counts in several such cases, in which the biopsy was the chief factor in explaining the condition

CASE 21—A 38 year old Negress was seen in consultation at the Provident Hospital She had marked enlargement of the liver and spleen and moderate enlargement of the lymph nodes The peripheral blood was nondescript, biopsy of the lymph nodes had not been made The marrow contained 17 per cent of "tissue cells" similar to the cells seen in small cell lymphosarcoma The biopsy effectively eliminated the working diagnosis of aleukemic leukemia

CASE 22—A 58 year old man entered the clinic because of severe pain in the back Roentgenograms disclosed a destructive lesion of the lumbar vertebrae The peripheral blood had a definite leukemoid reaction The sternal marrow contained clumps of basophilic erythroblasts, many of which were multinucleated and appeared neoplastic It was felt that a diagnosis of erythroblastic multiple myeloma was tenable

CASE 23—A 55 year old man was admitted to the hospital with an acute illness of several weeks' duration He suffered frequent nosebleeds, bleeding from the gums and rectum and great weakness The spleen and liver were not enlarged, nor were the lymph nodes Roentgen examination showed some tiny destructive lesions of the ribs The finding of "tissue cells," similar to round cell sarcoma cells suggested a diagnosis of lymphosarcoma The patient died promptly, and permission for autopsy was refused

CASE 24—A 58 year old man had had syphilis and received tremendous amounts of bismuth and mercury compounds He entered the clinic because of weakness and pallor He had severe anemia which resembled pernicious anemia in some respects Because of the history of syphilis and an enlarged liver, the diagnosis was deferred pending biopsy of sternal marrow The marrow was typical of pernicious anemia, and the subsequent successful course under liver therapy justified the diagnosis

CASE 25—A 21 year old Italian was referred to the clinic because he was anemic and had a peculiar yellowish color The most striking feature of his illness was the large number of nucleated red cells in the peripheral blood Biopsy disclosed such a predominance of these cells that despite the age of the patient a diagnosis of chronic erythroblastic anemia of the Cooley type was made Roentgenograms of the skull later disclosed a thickened, granular diploe like that associated with Cooley's anemia No therapeutic measure appreciably influenced the value for hemoglobin Splenectomy was performed and the histologic appearance of the spleen confirmed the diagnosis No special benefits except mechanical relief followed the splenectomy

CASE 26—A 48 year old man entered the hospital while recovering from severe pharyngitis A low white cell count, with many mononuclears, and some enlarged lymph nodes caused his physician to fear that acute leukemia was responsible for the illness The first biopsy of sternal material, revealing many myelocytes, seemed to confirm this view, but another one six days later gave such radically different results, as did examination of the peripheral blood, that we were

TABLE 6—*Differential Counts of the Peripheral Blood and the Sternal Marrow* † in Cases 21 to 26

Peripheral blood on day of biopsy	Case 21	Case 22	Case 23	Case 24	Case 25	Case 26
Hemoglobin, Gm per 100 cc	9.6	13.6	6.2	6.4	6.2	14.4
Red blood cells	1,100,000	3,790,000	2,230,000	1,480,000	1,380,000	4,700,000
White blood cells	18,000	12,000	22,300	4,300	19,200	3,200 13,000
Reticulocytes, per cent						
Polymorphonuclears	35	79	18	2.4	2.0	8 35
Lymphocytes	60	9	81	68	56	50 38
Monocytes	5	6	1	30	26	38 10
Eosinophils		1		2	16	
Basophils		1				
Myelocytes		1				
Metamyelocytes		1				
Band forms		4				
		2				
Sternal marrow					†	
Date					134 nucleated	
Myeloblasts					r b c 100 w b c	
Promyelocytes	0	30 11	10 12		1 yr	1/23 2/1
Myelocytes	30	03 43	0 03	0.6	01	40 10
Metamyelocytes	25	73 83	26 12	13	05 0	40 30
Band forms	35	136 102	16 12	15.0	40 28	37.0 12.5
Polymorphonuclears	25.0	210 206	10 23 }	15.4	01 50	45 12.0
All eosinophils	19.0	186 67	52 51 }	32.4	101 162	20 50.0
Basophils	30	23 40	0 01	0.6	70 0	10 15.5
Monocytes	0	0 0	0 0	0	02 0	0 0
Lymphocytes	0	0 0.4	0 06	0	0 0	0 0
Megaloblast series	80	56 35	40 30	0	02 0.2	0 10
Basophilic erythroblasts				1.2	35 07	60 3.8
Polychromatic and orthochromatic erythroblasts	25	43 37	52 05	68 73	38	15 10
Histiocytes	13.5	22.2 33.9	8.4 5.5	22.1	75 10	34.5 10
Megakaryocytes	0	0 1.0	1.0 0	0.2	53.0 41.0	0 0.5
Tissue cells	0	0 0.2	0 0	0.6	0	0
	17.0		68.0 78.0			

* The duplicate differential counts have same significance as in the other tables
† The patient had been receiving potent liver extract for eighteen hours

satisfied that what we were observing was agranulocytosis in the stages of vigorous spontaneous recovery. The patient remained well.

That biopsy of sternal marrow is useful as a scientific tool in the study of pernicious anemia is illustrated by two examples from our series of such patients who had biopsies before and shortly after receiving liver extracts. In case 24 (table 6), the potent extract was given eighteen hours before the second biopsy and no effect was apparent. However, the patient subsequently had a satisfactory reticulocyte response and a good hematologic recovery. The patient in case 27 (table 7) had received in the four days preceding the biopsy one and one-half vials of a potent liver extract and an indefinite number of

TABLE 7—*Differential Counts of Peripheral Blood and Sternal Marrow in Cases 27 to 28*

	Case 27		Case 28			
	1	2	1	2	3	4
Biopsy number						
Date	2/25	3/9	10/1	10/5	10/10	10/23
Peripheral blood on day of biopsy						
Hemoglobin, Gm per 100 cc	6.0	7.5	6.8	6.9	6.9	8.0
Red blood cells	1,580,000	1,810,000	1,990,000	1,900,000	2,100,000	2,890,000
White blood cells	5,500		4,000			
Reticulocytes, per cent	56	2	0.2	0.5	0.7	8.0
Sternal marrow						
Myeloblasts	0.4	0	1.2	1.1	1.0	0.6
Promyelocytes	1.0	0.8	3.1	3.0	2.1	1.5
Myelocytes	7.0	14.9	12.7	10.0	11.5	4.4
Metamyelocytes	8.0	14.2	6.4	4.5	7.0	8.7
Band forms	15.2	22.4	15.9	9.8	8.4	18.9
Polymorphonuclears	9.8	16.4	6.4	9.0	3.1	27.5
Lymphocytes	5.5	1.6	3.6	5.8	7.7	13.3
Basophils						
Megaloblasts						
Polychromatic and ortho-	} 0.8	1.6	{ 12.3	15.0	3.5	0
chromatic megaloblasts						
Basophilic erythroblasts	5.5	3.2	6.9	5.0	3.5	2.6
Polychromatic erythroblasts	20.2	8.2	6.4	4.6	30.7	9.8
Orthochromatic erythroblasts	21.4	6.0	6.5	5.0	3.8	6.4

capsules of extralin (a liver and stomach preparation). The reticulocytes were 56 per cent at the time of the first biopsy, and the marrow picture was that of a typical response to liver therapy. Case 28 (table 7) is an ideal illustration of this use of biopsy. Tissue for the first biopsy was taken before any medication had been given. The second biopsy was made after four days' trial of an experimental, supposedly anti-anemic product. In the five days after the second biopsy there was no evidence of reticulocytosis, a fact that was predicted on the basis of the unchanged megaloblastic picture after four days of treatment. Tissue for the third biopsy was taken fourteen and one-half hours after a potent extract derived from 300 Gm of liver had been given. The rise in reticulocytes provoked by this injection did not appear until the third day. The last biopsy was made thirteen days after the third one and revealed a complete transformation of the marrow to normal.

COMMENT

We have had unfortunately few cases in which the presence of abnormal cells in the material obtained by sternal puncture has aided us in diagnosis. Other workers⁴ have cited many such instances. Obscure examples of Gaucher's disease, malaria, carcinomatosis, multiple myeloma, trypanosomiasis and kala-azar have been elucidated by biopsy of sternal marrow, and in such cases the method finds its greatest value. The separation of the leukemoid states from true leukemia and the correct diagnosis of leukemia with minimal or no changes in the peripheral blood and no clinical findings⁵ is another field of usefulness for this technic. Cases 13, 22 and 26 illustrate the correct interpretation of leukemoid blood pictures. We have, strangely, seen no instances of leukemia in which the diagnosis was not established by other clinical means when the biopsy of sternal marrow was in itself diagnostic. The failure to obtain representative material is perhaps responsible for the few times when aid was anticipated and was not forthcoming.

The recognition of distinct dyscrasias of the blood solely by biopsy of sternal marrow is reported frequently⁶. These are generally aplastic

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5 Mettier, S. R, and Purviance, K. Leukemia Without Leukocytosis (Aleukemic Myelosis) and Without Splenomegaly, *Arch Int Med* **60** 458 (Sept) 1937.

6 Storti, E. Ueber ein Fall von lymphatischer Leukämie mit ausschliesslicher Lokalisation im Knochenmark und über die Bedeutung der Sternalpunktion für die Diagnose dieser Krankheitsform, *Deutsches Arch f klin med* **180** 612, 1937. Benhamou, E, Nouchy, A, and Cohen-Solal, G. Anémie aplastique précocement décelée par le médullogramme, *Sang* **11** 763, 1937. Fiessinger, N, Dupuy, R, and Laur, C. M. Les myelogrammes au cours des cirrhoses, *ibid* **11** 89, 1937. Freeman, W. Bone Marrow Studies in Glandular Fever, *Am J Clin Path* **6** 185, 1936. Santoianna, G. Primi risultati di ricerca in vivo sulla del midollo osseo nel corso di alcuna dermatosi, *Riforma med* **52** 1727, 1936. Kingery, L. B, Osgood, E. E, and Illge, A. H. Sternal Puncture. A Diagnostic Aid in Leukaemia Cutis, Possible Aid in Differentiating Lymphoblastomas, *Arch Dermat & Syph* **35** 910 (May) 1937.

anemia and megaloblastic anemia—as in pregnancy, infectious mononucleosis or leukemia cutis. In our series there were only 3 cases (24, 25 and 26) in which the diagnosis was made in this manner, and, curiously, except in case 25 a correct diagnosis would have been made by other clinical means in a few days.

The negative value of the biopsy of sternal marrow is large, and perhaps our greatest pleasure has been in cases in which the examination allowed us to reassure patients who were thought to be seriously afflicted. This negative usefulness, however, is mitigated by the frequency with which we encountered apparently normal marrow in the face of obviously severe disease.

It is our impression and belief that extremely thorough clinical investigation of patients robs biopsy of sternal marrow of much of its value. In our hands it has more commonly been a link, and often a superfluous link, in the diagnostic chain than it has been the sole means of establishing a diagnosis. The knowledge that potent products for the treatment of pernicious anemia convert the megaloblastic marrow to erythroblastic marrow within, usually, twenty-four hours is valuable in clinical research. It permits more rapid assaying of new remedies and allows one to expose his patients to a minimum of risk during the testing period. With severely anemic patients there is an obvious advantage in not waiting seven or ten days for the expected response from experimental therapy.

SUMMARY AND CONCLUSIONS

The technics for biopsy of marrow, the normal differential counts of material so obtained and the limitations of the methods are discussed.

Our experience is reviewed, and 28 examples illustrating the uses, benefits and disadvantages of biopsy of sternal marrow are presented.

It is indicated that thorough clinical investigation deprives the biopsy of sternal marrow of many of its uses.

The usefulness of this type of biopsy in clinical research, particularly in studies of pernicious anemia, is pointed out.

METASTATIC CALCIFICATION

REPORT OF TWO CASES

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Calcinosis is the term applied to a condition marked by a widespread abnormal deposition of calcium salts in various tissues of the body. In some conditions, such as dystrophic calcification, one must assume a previous retrogressive change in the tissues with subsequent deposition of calcium salts. In other conditions, however, the lime salts are deposited in previously healthy tissues. In the latter instance there are, owing to some still unexplained factor, mobilization of the calcium from the normal depots in bones and redistribution to various tissues and organs in the body. Oversaturation of the blood with calcium salts occurs in some cases. This condition was first recognized by Virchow,¹ who called it "metastatic calcification." Since then many reports have appeared in the literature.² Such calcification is not limited to any one condition but has been reported in association with a variety of diseases, such as scleroderma, dermatomyositis, nephritis, renal rickets, lipid dystrophies, leukemias and various diseases of the bone. Rothstein and Welt³ have recently published an excellent review of the literature with a report of 3 instances of calcification in children.

From the Department of Laboratories, Division of Pathology, the Jewish Hospital of Brooklyn

1 Virchow, R. Ueber Kalkmetastase, Virchows Arch f path Anat **8** 103, 1855

2 Pusitz, M E, Owen, A K, and Finney, G A. Calcinosis Cutis, J A M A **110** 360 (Jan 29) 1938. Gould, S E, and Raiford, F T. Calcinosis Universalis. Report of a Case with Autopsy Findings, Am J Roentgenol **39** 741, 1938. Widmann, B P, Ostrum, N H, and Freed, H. Practical Aspects of Calcification in the Various Body Tissues, Radiology **30** 598, 1938. Schatz, T. Diffuse Interstitial Calcinosis, *ibid* **22** 54, 1934. De Santo, D A. Metastatic Calcification in Myelogenous Leukemia, Am J Path **9** 105, 1933. Sheldon, J H. Calcinosis Universalis, Proc Roy Soc Med **27** 623, 1934. Hein, B J. Calcinosis Universalis, Arch Surg **26** 389 (March) 1933.

3 Rothstein, J L, and Welt, S. Calcinosis Universalis and Calcinosis Circumscripta in Infancy and Childhood. Three Cases of Calcinosis Universalis, with Review of the Literature, Am J Dis Child **52** 368 (Aug) 1936.

The present paper is a report of 2 cases. In 1 the condition was associated with leukemic myelosis, and in the other it complicated a normal pregnancy in an otherwise apparently healthy young woman. The widespread distribution of the lesions in these 2 cases prompted this report.

REPORT OF CASES

CASE 1—H. K., a 13 year old white girl, was admitted to the Jewish Hospital of Brooklyn on Nov. 19, 1934. She complained of weakness, pain

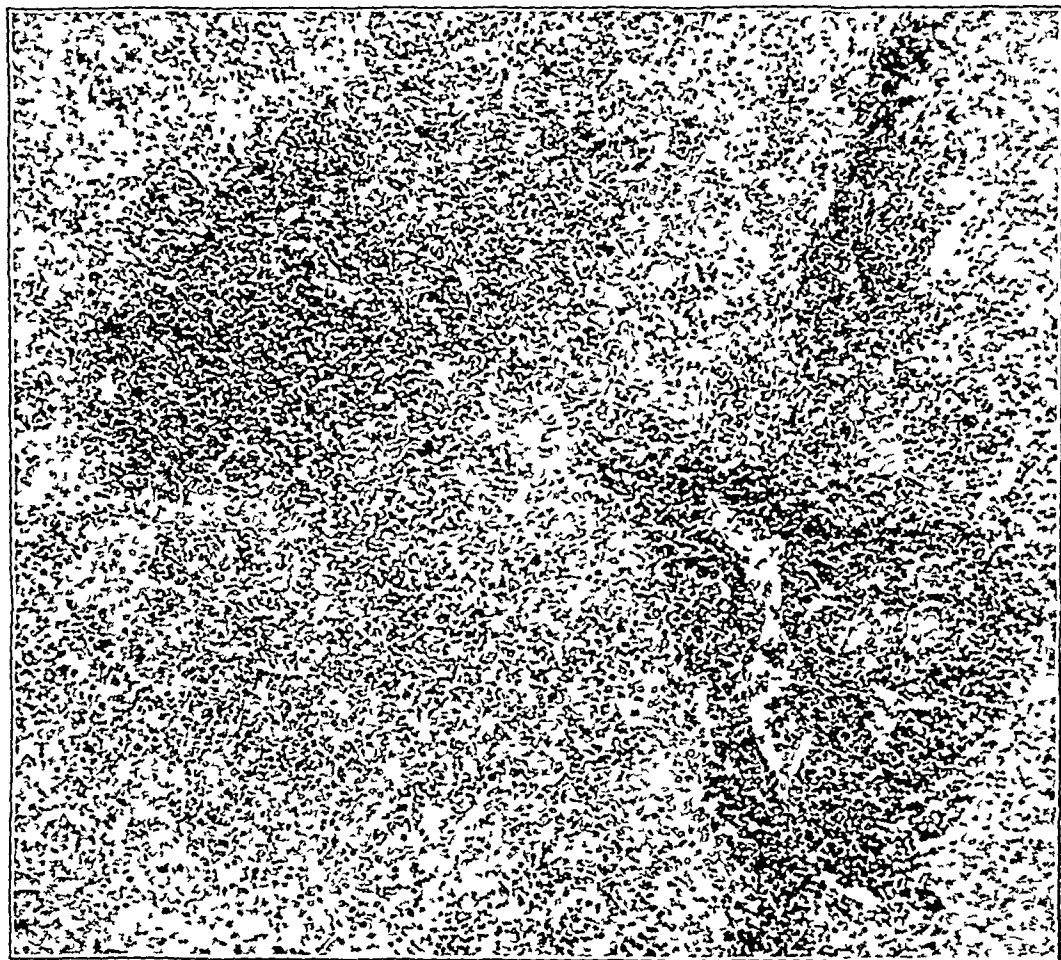


Fig. 1 (case 1)—Liver with leukemic infiltration. Hematoxylin and eosin; $\times 160$.

in the left flank for the past twelve hours, postprandial vomiting for the past month and loss of 25 pounds (11.3 Kg.) in the last two months. The family history was irrelevant.

Two months before the present admission the patient began to have pain which started in the thighs and radiated to the ankles and feet. Later it became localized in the right flank and was more severe. She spent three weeks in another hospital, where various studies were made but no definite diagnosis was arrived at. She was discharged unimproved. The pain in the right flank disappeared, but pain developed in the left flank and shortly there-

after in the lower two ribs in the axillas. Her loss of weight was due chiefly to the fact that she was afraid to eat because of the postprandial vomiting.

The temperature on admission was 98.6 F. The pulse rate was 95, the respiratory rate 16 and the blood pressure 140 mm of mercury systolic and 110 diastolic. The heart and lungs were normal. There was tenderness over the twelfth rib on the left side. The right kidney was palpable, and there was enlargement of the cervical, axillary, inguinal and abdominal lymph nodes. Electrocardiographic studies revealed myocardial and auricular involvement and sinus tachycardia. Roentgenographic studies of the chest, ribs, skull, hands and sella turcica showed



Fig 2 (case 1)—Kidney with leukemic infiltration. Hematoxylin and eosin.

these structures to be normal. There were rarefaction and mottling in the shaft of the fibula and in the thoracic and lumbar vertebrae. There were also punched-out semicystic formations below the heads of both humeri. While the patient was in the hospital the course was progressively downhill. She had convulsions and became semicomatose. She died on February 7.

Laboratory Data—Urinalysis revealed a fixed specific gravity of 1.008 to 1.010, a trace of albumin and a few hyaline casts but no red blood cells. The phenolsulfonphthalein test showed a total excretion of 27 per cent. A blood count showed red cells, 3,400,000 per cubic millimeter, white cells, 6,300 per cubic millimeter, with 85 per cent polymorphonuclear neutrophilic leukocytes and 15 per cent lymphocytes. The hemoglobin content was 60 per cent.

A study of the blood chemistry on December 10 gave the following values: chlorides, 424 mg, nonprotein nitrogen, 101 mg, total proteins, 6.22 mg, albumin, 3.47 mg, globulin, 2.75 mg, cholesterol, 197 mg, sugar, 134 mg, calcium, 20.6 mg, and phosphorus, 4.7 mg, per hundred cubic centimeters. The value for phosphatase was 4.5 units, the carbon dioxide content 53.5 volumes per cent and the albumin-globulin ratio 1.26. The Wassermann reaction was negative.

Clinically the condition was thought to be aleukemic myelosis.

Necropsy—The body was well developed but poorly nourished. There was no excess fluid in the peritoneal or pleural cavities.

The heart weighed 210 Gm. The right side of the heart and the valves showed nothing of note except slight thickening at the bases of the aortic



Fig 3 (case 1)—Lung with calcification in the walls of the veins and in the parenchyma. Hematoxylin and eosin.

cusps. In the left atrium there were numerous small, sharply defined calcific plaques beneath the endocardium.

The lungs were solid, numerous irregularly shaped hard nodules could be palpated throughout. The surfaces were smooth and mottled yellow-red and purple-blue. The cut surfaces were granular, the color was a peculiar yellow with scattered areas of pink. In the areas of hardening there were gritty yellow plaques presenting the appearance of a honeycomb. The larger branches of the pulmonary artery were calcified. Histologic examination revealed calcium deposits in the walls of alveoli, in the walls of some bronchi immediately beneath the basement membrane of the lining epithelium and in the intima of many veins and some arteries. There was no evidence of any inflammatory reaction in the calcified areas.

The spleen weighed 580 Gm. It was firm and red. In the cut surfaces the malpighian bodies were prominent. Irregular patches of yellow were distributed throughout the deep red pulp. Histologically there was widespread leukemic infiltration of the organ.

Leukemic infiltration was also noted in the liver, kidney, thymus gland, pancreas, lymph nodes and bone marrow of the ribs and vertebrae.

Minute areas of calcification were present in the adrenal glands, kidneys and thymus gland.

The parathyroid glands were small and presented nothing of note.

The anatomic diagnosis was leukemic myelosis in the bone marrow, lymph nodes, spleen, liver, kidneys, pancreas and thymus gland, metastatic calcification

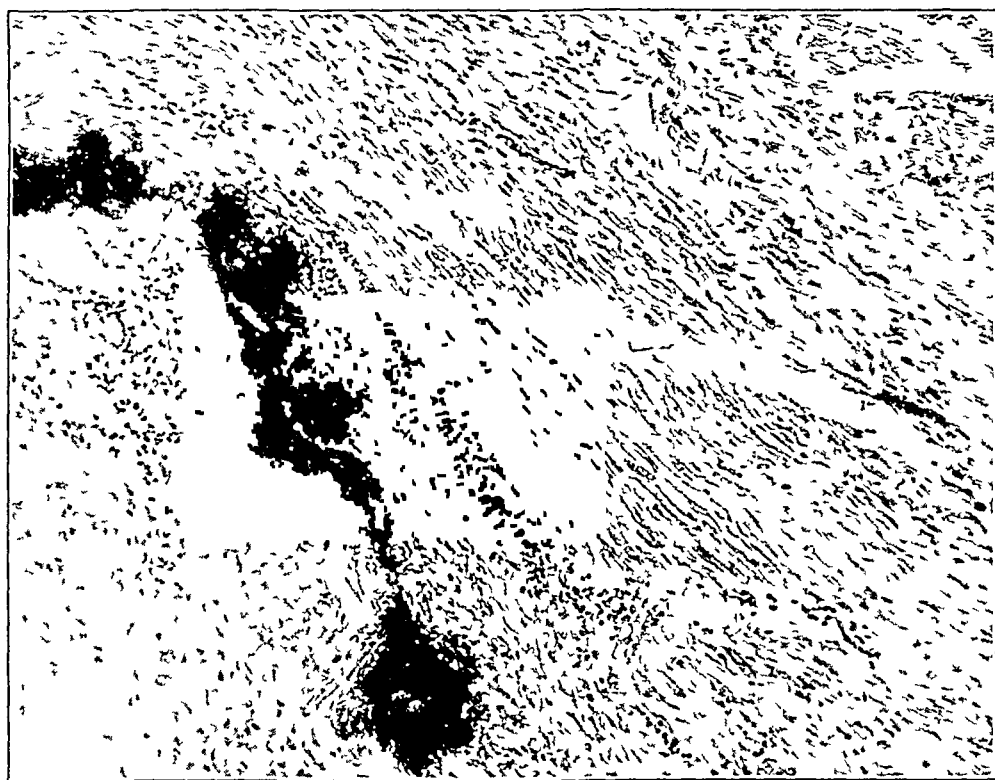


Fig 4 (case 1) —Calcium deposits about the vessels in the wall of the left auricle. Hematoxylin and eosin, $\times 150$

in the lungs, left atrium, adrenal glands, kidneys, thymus gland and some of the moderate-sized arteries.

CASE 2—H. K., a 25 year old white woman, was admitted to the Jewish Hospital of Brooklyn on Oct 17, 1937, complaining of weakness, dizziness, cough, anorexia and fever for the past six weeks. The family history was irrelevant.

The patient had had chorea at the age of 15 years. The condition lasted for three or four months. For some time afterward she had occasional attacks of involuntary twitching. There was no history of cardiac involvement. She had been married for six years and had two children, a boy aged 5 years and another aged $1\frac{1}{2}$ months.

About the seventh month of her second pregnancy, which terminated on September 1 in a spontaneous normal delivery, the patient began to complain of a dry, irritating cough. At home, after her discharge from the hospital, she complained of weakness, lassitude, cough and frequent attacks of vertigo. The weakness persisted, and two weeks prior to admission she consulted a physician, who found pus in her urine and treated her for "inflammation of the kidneys." The patient at no time complained of chills, pain in the back or in the lumbar regions, dysuria, hematuria or frequency of urination. She had no pains in the chest, no hemoptysis and no night sweats. Her cough was productive of a moderate amount of white sputum. On the day prior to admission her temperature rose to 104 F, and she was advised to come into the hospital.

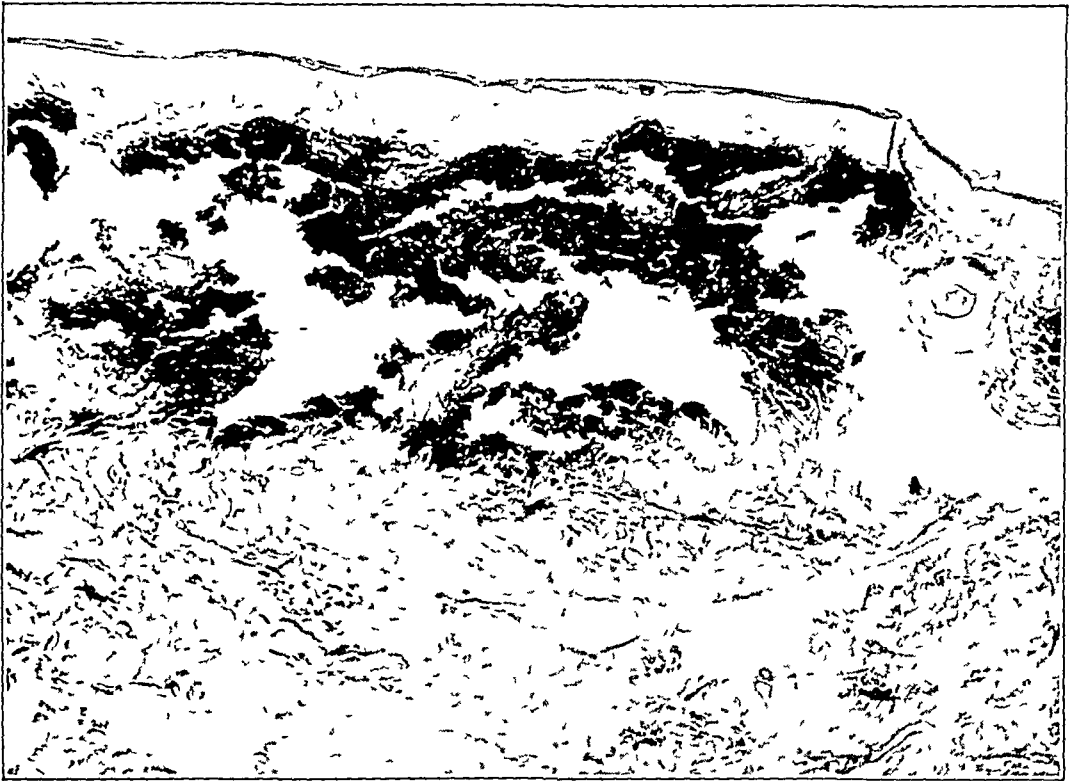


Fig 5 (case 2) —Cutaneous lesion with extensive calcification in the upper layers of the cutis. Hematoxylin and eosin, $\times 45$

On her admission the temperature was 100.4 F, the pulse rate 120, the respiratory rate 20 and the blood pressure 124 mm of mercury systolic and 60 diastolic. The heart was not enlarged. The sounds were of good quality, the beat was rapid but regular. The lungs on percussion were resonant except at the base of the right lung posteriorly, this region was dull to flat up to the angle of the scapula. Over this area the tactile fremitus was diminished. The breath sounds were vesicular but markedly diminished over the base of the right lung. There were no rales or friction rub. The liver was enlarged and moderately tender. Its edge was firm and was palpable 5 fingerbreadths below the costal margin. The spleen was not palpable. There was marked tenderness in localized areas along the tibias. There were no swellings or masses in these areas. The reflexes were hyperactive but equal.

Roentgenograms taken on the day after the patient's admission to the hospital revealed the presence of fluid at the base of the right lung. Thoracentesis was performed two days later, and 60 cc of clear straw-colored fluid was obtained. Similar fluid was obtained on several occasions during the patient's stay in the hospital, at times as much as 1,700 cc. During this time the temperature ranged from 100 to 102 F, with an occasional rise to 104 F. On November 13 there appeared at the periphery of each breast a lesion characterized by thickening of the skin and well circumscribed smooth pearly nodules. The following day there were numerous yellow indurated nodules in both axillas, at the periphery of each breast and over the right tibia. These ranged from the size of a millet seed to that of a hazelnut. They were irregularly oval and were not tender. Some of the lesions had coalesced and become hard cardboard-like plaques. The cutaneous lesions progressed and three



Fig 6 (case 2) —Lung with edema and calcification of the wall of the vessel and calcification of the parenchyma. Hematoxylin and eosin, $\times 75$

days later were present in both groins, extending along the inner aspects of both thighs. The temperature rose to 104.8 F. The patient became markedly dyspneic and cyanotic. The cardiac rate was rapid, and the sounds were of poor quality. There was dependent edema in the sacral region and in the lower extremities. Tissue from a cutaneous lesion, taken for biopsy on November 19, was described as "skin with atrophy." The course thereafter was rapidly downhill. The cutaneous lesions had advanced to involve both inguinal regions, extending upward over the iliac crests and downward along the medial and posterior aspects of the thighs to the knee of the right leg and to the midcrural region on the left leg. The patient became semistuporous on November 26. The temperature rose to 105 F, the pulse rate rose to 150 and the pulse was weak. Fluid was present at the bases of both lungs. On the following day there was Cheyne-Stokes respiration, the cyanosis increased, and the patient died at 9:30 p m.

Laboratory Data—Urinalysis on October 27 showed an acid urine with a specific gravity of 1.016, a 1 plus reaction for albumin and no sugar. Numerous white blood cells were observed on microscopic examination. The blood count was as follows: hemoglobin, 53 per cent, red cells, 3,400,000 per cubic millimeter, white cells, 6,700 per cubic millimeter, polymorphonuclear leukocytes, 78 per cent, lymphocytes, 14 per cent, monocytes, 4 per cent, and band forms, 4 per cent. On November 8 the white cell count rose to 24,400 per cubic millimeter, with 64 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, 20 per cent band forms and 4 per cent monocytes. A complete study of the blood chemistry gave the

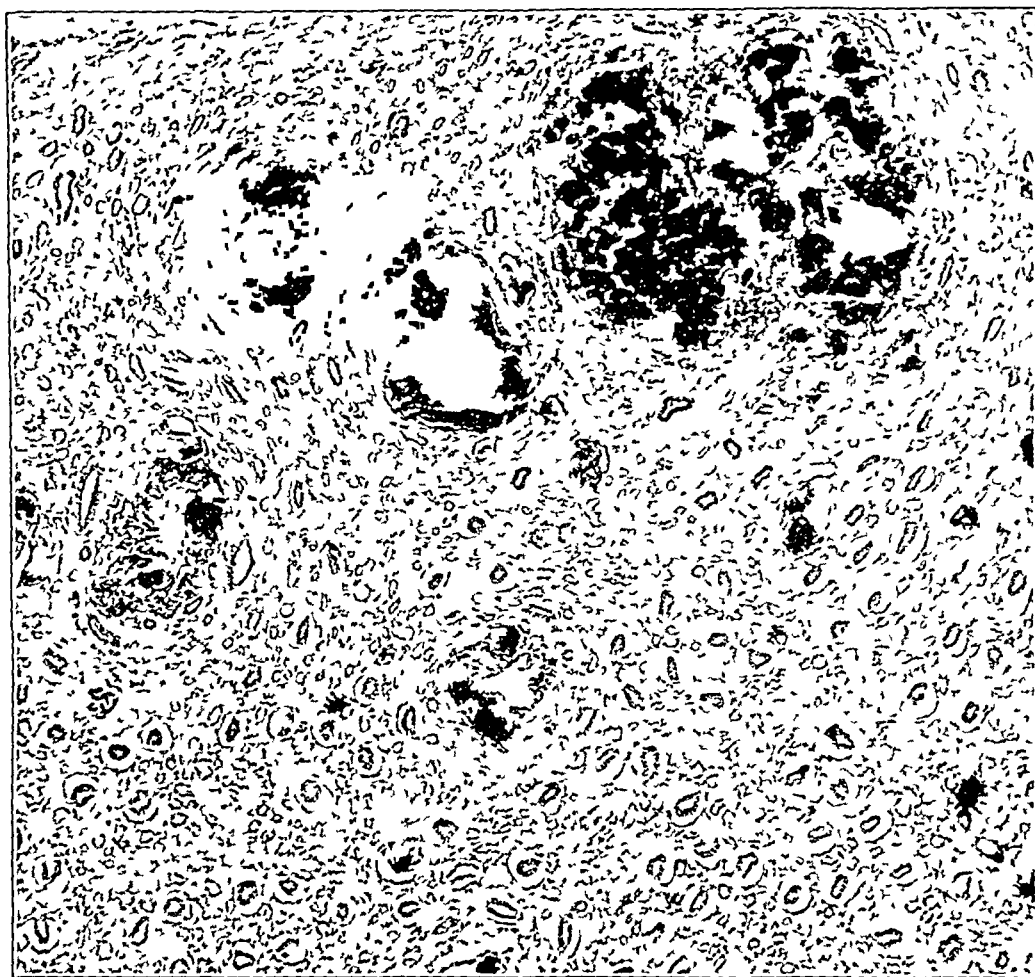


Fig 7 (case 2) —Kidney with metastatic calcification. Hematoxylin and eosin; $\times 60$

following values: sugar, 112 mg; urea, 711 mg; uric acid, 96 mg; total proteins, 467 mg; albumin, 226 mg; globulin, 241 mg; cholesterol, 154 mg; free cholesterol, 82 mg; total lipids, 614 mg; chlorides, 316 mg; calcium, 156 mg; phosphorus, 35 mg; total base, 140 mg; sodium, 280 mg; and phosphatase, 82 units. The carbon dioxide content was 65.5 volumes per cent. The albumin-globulin ratio was 0.94. The icterus index was 3.6. The Kline reaction was negative. Repeated cultures of the blood gave negative results. The sedimentation rate was 210 mm per hour.

Examination of bone marrow obtained by aspiration on November 2 showed myeloblasts, 4; myelocytes, 35; eosinophilic myelocytes, 4; metamyelocytes, 4;

stab forms, 8, polymorphonuclear leukocytes, 30, eosinophils, 5, granulocyte-lobocyte ratio, 65 35, granulocyte-erythroblast ratio, 80 20, ratio of early to later erythroblasts, 25 75, and white blood cells per high power field, 8

A concomitant smear of the peripheral blood showed stab forms, 5, polymorphonuclear leukocytes, 59, lymphocytes, 28, monocytes, 4, eosinophils, 4, and platelets, 3 plus There were anisocytosis (2 plus), microcytosis (3 plus), macrocytosis (2 plus) and polychromasia (2 plus)

By a study of the bone marrow and a smear of the peripheral blood leukemic myelosis was excluded

Necropsy—The body was well developed but poorly nourished Around the outer margins of both breasts the skin was pale brown, leathery and raised above the surface, the condition extended into the axillas and was also present over

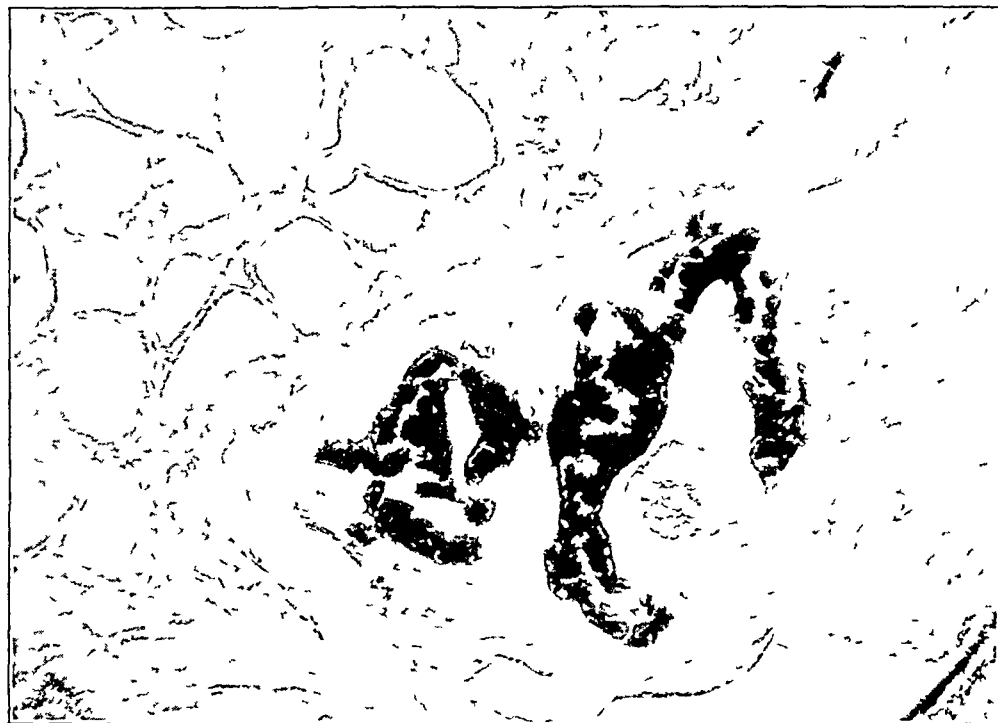


Fig 8 (case 2)—Thyroid gland with edema and calcium deposits in the wall of the vessel Hematoxylin and eosin, $\times 75$

the anterior aspects of both forearms Within the affected areas were old scars and small raised nodules of cardboard-like consistency Similar lesions were present over both thighs and legs There was a large decubitus ulcer over the right greater trochanter There was edema of the labia majora and of the lower extremities There was 100 cc of blood-tinged fluid in the peritoneal cavity, and 1,000 cc of similar fluid was present in each pleural cavity

The heart weighed 260 Gm The right side was not unusual In the left atrium the endocardium was studded with numerous firm, calcific yellow-white plaques Similar plaques were also present in the aortic cusp of the mitral valve The cusps of the aortic valve were somewhat shortened and slightly thickened

The aortic valve ring was calcified in places The coronary arteries were widely patent They cut with a gritty sensation In the intimal surfaces were

seen numerous small firm yellow plaques. The aorta and pulmonary arteries were elastic and except for occasional atheromatous patches showed nothing of note.

The lungs were heavy, weighing about 600 Gm each. They did not collapse when the thoracic cavity was opened. The external surfaces were smooth, glistening and mottled with pink and purple-red. The cut surfaces were pink, with occasional raised red areas. There was a granular feel to the cut surfaces. The vessels stood out prominently.

The spleen weighed 190 Gm. It was soft and deep red on section. The malpighian corpuscles and fibrous markings were prominent. There were three small recent infarcts near the surface.



Fig 9 (case 2) —Mammary gland with vascular changes. Hematoxylin and eosin, $\times 82$.

Grossly there was little of note in the other organs except for marked congestion of the vessels and scattered petechiae. The liver had the typical nutmeg appearance. The kidneys weighed 160 Gm each. The capsules stripped with ease, leaving smooth surfaces over which were scattered small petechiae. The cortex and medulla were well demarcated. There was evidence of slight cystitis and slight proctitis. Small calcified plaques were present over the vocal cords. The thyroid gland was small and not unusual. The parathyroid glands, of which there were three, were also small.

Microscopic Examination—The striking picture in the various preparations from the different organs was seen in the veins and smaller arteries. The lumens were somewhat diminished owing to edema of the subintimal fibrous connective tissue. Within the intima there were fairly extensive deposits of calcium. In some vessels these deposits were also present in the media and even in the

adventitiae In the lungs, in addition to these vascular changes, there were calcium deposits in the bronchial walls immediately beneath the epithelial layer, in the walls of some alveoli and within the peribronchial and perivascular connective tissue The lungs also showed areas of pneumonia In the kidneys calcium deposits were seen not only in the vessels and in the walls of the tubules but also within the tubules and scattered widely through the interstitial connective tissue

Similar changes were seen in the vessels of the breasts, pancreas, spleen, uterus, cervix uteri and thyroid gland, as well as in the smaller branches of the mesenteric vessels

In the skin extensive calcium deposits were seen in the midcutis, apparently affecting primarily the elastic tissue fibers

The parathyroid glands histologically were not unusual

Analysis of a cutaneous plaque gave the following values calcium, 114 mg, phosphorus, 16 mg, total lipid, 0.2813 Gm, total cholesterol, 0.935 mg, and free cholesterol, 0.62 mg, per gram of tissue Analysis of normal skin gave the following results calcium, 0.1 mg, phosphorus, 1.1 mg, and total lipid, 7.4 mg, per gram of tissue

All the calculations were done on the dry basis

The anatomic diagnosis was metastatic calcification in the skin, heart, lungs, spleen, pancreas, kidney, uterus, breast, thyroid and larynx, generalized purpura, focal myocarditis, dilatation of the heart, bilateral hydrothorax, ascites, edema of the labia majora and the lower extremities, passive congestion of the viscera, bilateral focal pneumonia, cystitis, proctitis, infectious splenomegaly, and infarcts of the spleen

Two general types of pathologic calcification occur in the human body, the dystrophic type, in which the lime salts are deposited in previously diseased tissue, and the other, in which the salts are deposited in apparently healthy tissue The latter is subdivided by some into calcinosis universalis, in which there is no increase of calcium in the blood, and metastatic calcification, in which there is hypercalcemia The latter distinction appears to be unnecessary since in both instances the cause of the condition is little understood and since both types are associated with a variety of diseases Moreover, as in a case cited by Shelling,⁴ the concentration of serum calcium in the same patient may vary between normal and tetanic values

Since no degenerative changes precede the deposition of calcium salts in the various tissues, the cause must be sought in the general factors responsible for calcium and phosphorus metabolism in the body and for demineralization of the skeleton Some of the suggested causes are disturbances in the vascular supply to the part, disturbances in the calcium and phosphorus metabolism, disturbances in the acid-base equilibrium due to loss of carbon dioxide in the tissues,⁵ endocrine

⁴ Shelling, D. H. *The Parathyroids in Health and in Disease*, St. Louis, C. V. Mosby Company, 1935, p. 39

⁵ Wells, H. G. Calcification and Ossification, *Arch. Int. Med.* **7**: 721 (June) 1911, Metastatic Calcification, *ibid.* **15**: 574 (April) 1915

changes, hypervitaminosis D, infections and trauma Ham⁶ concluded that in metastatic calcification there is inability of the blood to retain the calcium in solution The level of diffusible calcium, therefore, is more important than the level of total calcium

SUMMARY

Two cases of metastatic calcification are reported In the first the condition was associated with a leukemic myelosis, in the second it complicated a normal pregnancy in an apparently healthy young woman The cause was not determined

6 Ham, A W Mechanism of Calcification in Heart and Aorta in Hypervitaminosis D, Arch Path **14** 613 (Nov) 1932

Progress in Internal Medicine

BLOOD

A REVIEW OF THE LITERATURE

CYRUS C STURGIS, M D

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S MILTON GOLDHAMER, M D

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FRANK H BETHELL, M D

ANN ARBOR, MICH

(Concluded from page 1231)

ANEMIA OF PREGNANCY

Experimental studies of the effects on the blood of iron deficient diets given to rats throughout gestation and lactation have been discussed earlier in this review,¹⁵⁹ A macrocytic form of anemia in pregnant rats has been produced by Kyer and Bethell¹⁶⁰ by means of diets deficient in protein. Such anemia is accompanied by characteristic changes in the percentage and absolute number of the nucleated cells in the several stages of erythrocytic development represented in the marrow.¹⁶¹ The specific alteration in erythropoiesis is a "shift" to the more immature nucleated red blood cells, analogous to the "megaloblastic block" found in the marrow of patients with pernicious anemia. In rats receiving an inadequate amount of protein during gestation there is also extensive lipoidosis of the liver, arising first in the central zones of the hepatic lobules. An etiologic relation between hepatic damage, induced by deficient diets, and specific changes in the marrow and circulating blood was suggested.

Bussabarger and his associates¹⁶² studied the effects of gastrectomy on the blood values of 5 dogs observed throughout fifteen pregnancies. Marked anemia developed during the course of eleven gestations, and a decrease in total circulating hemoglobin occurred regardless of changes

¹⁵⁹ Alt¹³⁷ Parsons, Hickmans and Finch¹⁴¹

¹⁶⁰ Kyer, J, and Bethell, F H. Production of Macrocytic Anemia in the Pregnant Rat by Diets Low in Protein, Arch Path **25** 761 (May) 1938

¹⁶¹ Bethell, F H. Studies of the Bone Marrow and Liver in Experimental Anemia of Pregnancy, Arch Path **25** 764 (May) 1938

¹⁶² Bussabarger, R A, Cuthbert, F P, and Ivy, A C. Studies on the Anemia of Pregnancy in Gastrectomized and Normal Dogs, J Lab & Clin Med **24** 24, 1938

in the total blood volume. The authors also observed the blood values of 12 normal dogs during pregnancy and found severe anemia in only 1 instance. In normal animals, lowering of the erythrocyte and hemoglobin levels was more pronounced in the puerperium than during gestation. Blood volume determinations for 8 dogs disclosed hydremia incidental to pregnancy in only 3 instances. Anemia in pregnancy following gastrectomy was of either normochromic or hypochromic type, and its development was attributed largely to a deficiency of reserve stores of blood-building materials.

Copper and iron determinations for human maternal and fetal blood were reported by Sachs and his co-workers¹⁶³. They found the whole blood iron content of the newborn to be high, whereas the copper value was uniformly low. On the other hand, the maternal blood iron content was normal or reduced, but the copper content was relatively high. The authors pointed out that large amounts of copper are stored in the fetal liver.

The important subject of changes in the blood volume which occur in healthy pregnant women was reinvestigated by Thomson and his associates,¹⁶⁴ who employed in their studies the azo dye Evans blue, and the Evelyn photoelectric microcolorimeter. They found a progressive increase in the plasma and the total blood volume, beginning early in pregnancy and reaching a maximum during the ninth lunar month. During the tenth lunar month a definite decrease in both the plasma and the total blood volume begins, which by the end of the second postpartal week brings the values close to the average normal level for nonpregnant women. The authors found in normal pregnancy a maximum increase in plasma volume of 65 per cent. According to them an absolute increase in the total cell volume also occurs but, proportionately, to a less degree. The increases in the plasma and the total blood volume determined by these workers are considerably greater than those reported by other investigators, and their results await confirmation.

Odefey¹⁶⁵ found a 40 per cent incidence of hemoglobin values below 12 Gm per hundred cubic centimeters in 103 women observed during pregnancy. Most of the cases he considered as representing "pseudoanemia," since the women were in apparent good health and their blood values, in the absence of therapy, returned to the normal range for non-

163 Sachs, A., Levine, V. E., Griffith, W. O., and Hansen, C. H. Copper and Iron in Human Blood. Comparison of Maternal and Fetal Blood After Normal Delivery and After Cesarean Section, *Am J Dis Child* **56** 787 (Oct) 1938.

164 Thomson, K. J., Hirsheimer, A., Gibson, J. G., Jr., and Evans, W. A., Jr. Studies on the Circulation in Pregnancy. III. Blood Volume Changes in Normal Pregnant Women, *Am J Obst & Gynec* **36** 48, 1938.

165 Odefey, R. Weitere Untersuchungen über die Pseudoanämie in der Schwangerschaft, *Zentralbl f Gynak* **62** 1981, 1938.

pregnant women after delivery Foderl¹⁶⁶ also described "pseudo-anemia" and differentiated it from "essential anemia of pregnancy," which he stated is a true iron deficiency anemia, being responsive to iron therapy He discussed pernicious anemia of pregnancy, which usually responds well to the administration of liver extract and iron and only rarely requires blood transfusion A third and rare form of anemia of pregnancy mentioned by this author was described as normocytic and is believed to be of the aplastic type It is associated with toxemia, and its presence is an indication for blood transfusion Most observers believe that the rare grave anemias accompanying toxemia are generally hemolytic rather than aplastic Ramsay and Thierens¹⁶⁷ studied the chemistry of the blood during pregnancy and found hemoglobin values below 9.7 Gm per hundred centimeters in 26 per cent of their series of about 100 patients Watson¹⁶⁸ stated that the physiologic lowering of the hemoglobin value in pregnancy may reach 7.7 Gm, but his evidence that these low values are actually normal was inconclusive

Reid and Mackintosh¹⁶⁹ determined the hemoglobin values for 1,094 women of poor social circumstances and attempted to ascertain the influence of anemia on the subsequent history of the mother and child Of the women studied, 10.2 per cent suffered from hypochromic anemia, according to the authors' criterion of normality for pregnancy, a minimum hemoglobin level of 9.7 Gm per hundred centimeters They found that the incidence of anemia was inversely proportional to the family income Anemia alone appeared to have a slight influence on the stillbirth rate, and anemia combined with poor social circumstances exerted a definite influence on neonatal and infant death rates and on infant morbidity rates Mothers who had suffered from anemia during pregnancy were not handicapped in establishing breast feeding but were less able to maintain lactation than nonanemic mothers No relation was apparent between anemia and toxemia, an abnormality or prolonged duration of labor or the birth weight of the infant

Napier and Majumdar¹⁷⁰ reported their analyses of the blood and the results of therapy in 57 cases of anemia in pregnant tea-garden coolie

166 Foderl, V Zur Differential Diagnose und Therapie der Schwangerschaftsanamien, Wien klin Wchnschr **51** 168, 1938

167 Ramsay, G, and Thierens, V T The Composition of the Blood in Pregnancy, Brit M J **1** 1199, 1938

168 Watson, H G The Blood Picture of Pregnancy, Am J Obst & Gynec **35** 106, 1938

169 Reid, W J S, and Mackintosh, J M The Influence of Anemia and Poor Social Circumstances During Pregnancy on the Subsequent History of Mother and Child, Lancet **2** 1389, 1937

170 Napier, L E, and Majumdar, D N Haematological Studies in Indians The Analysis of the Haematological Findings in Fifty-Seven Cases of Anaemia in Pregnant Tea-Garden Coolie Women, with Special Reference to the Results of Treatment, Indian J M Research **26** 541, 1938

women. The anemia was usually hypochromic or normochromic, 3 patients had a hyperchromic blood picture. Etiologic factors were the universal incidence of hookworm infestation and marked dietary deficiencies in these women. Protein, calcium and vitamins B and C were especially deficient. Treatment consisted of the administration of 1.2 to 1.6 Gm of iron as ferrous sulfate daily, 4 cc of autolyzed yeast three times a day and, in the presence of hyperchromic anemia, 2 cc daily of liver extract by intramuscular injection. Chappell and Bivings¹⁷¹ studied the blood of 329 pregnant Negroes and compared the findings with those obtained for 75 nonpregnant Negro clinic patients. The hemoglobin range was low, and the color index was reduced in most of the cases studied, but the hemoglobin values for the nonpregnant subjects averaged only 9.0 Gm per hundred centimeters, and the average level in pregnancy was 8.8 Gm. Poor results were obtained from iron therapy, parenteral administration of liver extract and treatment with supplementary vitamins A and D, and the authors emphasized the inadequacy of the diets of the group investigated.

A series of 100 patients with anemia of pregnancy was reported on by Stevenson¹⁷². Of these, 30 were said to possess the blood findings of pernicious anemia of pregnancy, 27 of those with pernicious anemia were multiparae and 28 were of a very low economic status. Nutrition was generally inadequate, the symptoms of anemia developed in most instances between the sixth and the eighth month but in 3 cases not until the puerperium. An icteric tinge of the skin was present in 24 of these cases, pyrexia in 19, glossitis in 15, splenomegaly in 15 and achlorhydria in 3. The excretion of urobilinogen was increased in 10 cases. Involvement of the central nervous system was not found. Good therapeutic results, including reticulocyte responses, were obtained from the use of liver, liver extract and desiccated stomach. The 70 other members of the group all suffered from anemia of the hypochromic type and responded satisfactorily to iron therapy.

Cases of severe macrocytic or "pernicious anemia" of pregnancy have also been reported recently by Dockeray,⁷⁴ Abramson¹⁷³ and Barnum Woodward¹⁷⁴.

POISONS, PHYSICAL AGENTS

Wood⁸⁹ found that of 522 patients treated with sulfanilamide 21 had acute anemia (children, 8.3 per cent, adults, 2.4 per cent). No pre-

171 Chappell, A., and Bivings, L. Anemia and Pregnancy. A Three Year Study on Negro Women, South M J **31** 876, 1938.

172 Stevenson, E. M. K. Anaemia in Pregnancy and the Puerperium, Tr Edinburgh Obst Soc, 1937-1938, p 81, in Edinburgh M J, July 1938.

173 Abramson, L. Etats rappelant l'anémie pernicieuse durant la grossesse et les suites de couches, Acta med Scandinav **96** 319, 1938.

174 Barnum, C. G., and Woodward, J. C. Severe Hyperchromic Macrocytic Anemia of Pregnancy, J A M A **111** 1749 (Nov 5) 1938.

disposing factors could be determined. The earliest signs of anemia were noted from twenty-three to seventy-two hours after the start of the therapy. The anemia was worst usually on the fifth day (third to seventh day). It was hemolytic and recurred in 4 of 5 patients during a second course of sulfanilamide therapy.

Campbell¹⁷⁵ did not encounter anemia or depression of the bone marrow in his series of patients treated with sulfanilamide, and concluded that "personal idiosyncrasy" is an important factor in the cases of involvement of the bone marrow reported by others.

The case reported by Ginsberg and Brams¹⁷⁶ illustrated the rapidity with which hemolytic anemia secondary to sulfanilamide therapy can develop. After four days of therapy (160 grams [10.4 Gm]), icterus was noted, and the red blood cell count on the seventh day had fallen from 4,500,000 to 1,100,000 red blood cells per cubic millimeter (hemoglobin, 25 per cent, leukocytes, 36,900 per cubic millimeter, neutrophils, 66 per cent). Recovery followed three blood transfusions (500 cc each) on successive days. Nelson and Scott-Young¹⁷⁷ and Wood⁸⁹ also reported cases in which hemolytic anemia followed sulfanilamide therapy.

In some persons who were cyanotic from sulfanilamide therapy, Posner, Guthrie and Mattice¹⁷⁸ found an abnormal blood pigment, having the same absorption band as methemoglobin. The band disappeared on saturation with carbon monoxide or dilution with water. The pigment was unstable, slowly reverting to normal blood pigment.

In patients treated for fourteen days with 21 Gm of sulfanilamide, Britton and Howkins¹⁷⁹ found that 46 per cent showed neutropenia and 44 per cent transient monocytosis. The lowest count was noted at the end of the second or at the beginning of the third week. However, the toxic symptoms, present in 70 per cent of the patients, showed no direct relation to the variation in the leukocyte count.

Weil, Perlés and Aschkenasy¹⁸⁰ studied the blood of 54 patients with anemia of benzene poisoning. The blood characteristics were hypochromia, leukopenia, neutropenia, eosinophilia (4 to 8 per cent in 30

175 Campbell, C. M. Effect of Sulfanilamide on the Blood Picture, *Lancet* **1** 247, 1938.

176 Ginsberg, A. M., and Brams, J. B. Acute Hemolytic Anemia Following Treatment with Sulfanilamide, *J. Missouri M. A.* **35** 174, 1938.

177 Nelson, E. L., and Scott-Young, M. Profound Anemia Following Administration of Sulfanilamide in Acute Gonorrhea, *M. J. Australia* **1** 626, 1938.

178 Posner, I., Guthrie, N. W., and Mattice, M. R. Formation of Abnormal Blood Pigment as Complication of Sulfanilamide Therapy, *J. Lab. & Clin. Med.* **23** 804, 1938.

179 Britton, C. J. C., and Howkins, J. Action of Sulfanilamide on Leukocytes. Report of Fifty Ambulant Patients, *Lancet* **2** 718, 1938.

180 Weil, P. E., Perlés, S., and Aschkenasy, A. Etudes sur le benzolisme latent, *Sang* **12** 151, 1938.

per cent of the cases), thrombopenia, clotting defects and capillary fragility. The latent form is an aplastic anemia. The authors made a plea for well ventilated rooms, limited hours of work and regular medical inspection of workers in benzene.

In a case of benzene poisoning, Gall¹⁸¹ found aplastic anemia, leukopenia, thrombopenia and macrocytosis. The peripheral circulation, however, showed reticulocytes, nucleated red blood cells and immature myeloid cells, secondary to massive myeloid (erythropoietic) metaplasia in the spleen and, to a less extent, in the liver. Zolezzi¹⁸² found decreased gastric function accompanying anemia in 8 cases of benzene poisoning in workers in the rubber industry. He also noted several cases of anemia among leather workers in shoe factories due to adhesives and mastics dissolved in benzene. In Kern's¹⁸³ case of benzene poisoning, there was a selective reduction in the number of blood platelets, with disappearance from the blood. Later there was an increase to above normal, but the red and white blood cells did not appear to be involved in the process. Neurologic symptoms, presumably secondary to hemorrhage into the central nervous system, were present. Tara¹⁸⁴ described chronic benzene poisoning in 14 pregnant women. Of these, 4 had normal deliveries, 3 had difficult deliveries, with uterine inertia, 1 gave birth to a dead child, and 7 had abortions.

Rajam and Tampi¹⁸⁵ noted 3 cases of blood dyscrasia after treatment with arsphenamine and similar agents in 18,620 cases of syphilis (64,101 injections). One patient had thrombopenic purpura (platelets, 50,000). The second patient had aplastic anemia and the third granulocytopenia. Treatment included the use of epinephrine, calcium, thiosulfate, liver preparations, pentnucleotide and repeated transfusions. Arsenical injections must be discontinued, as recurrences are invariably fatal. Kadın¹⁸⁶ reported 3 cases of aplastic anemia with severe damage to the bone marrow in patients who had been treated with arsphenamine. All the patients showed a hemorrhagic tendency.

In pregnant female rats Briese¹⁸⁷ produced anemia by means of inhalation of carbon tetrachloride. Macrocytic anemia, with an increased

181 Gall, E. A. Benzene Poisoning with Bizarre Extramedullary Hematopoiesis, *Arch Path* **25** 315 (March) 1938.

182 Zolezzi, G. G. Alterazione del chimismo gastrico nella intossicazione da benzolo, *Med d lavoro* **28**:275, 1937.

183 Kern, B. Isolierte-Thrombopenie durch chronische Benzolvergiftung, *Munchen med Wchnschr* **85** 1062, 1938.

184 Tara, S. Le benzénisme larvé chez la femme enceinte, *Sang* **12** 352, 1938.

185 Rajam, R. V., and Tampi, R. B. Postarsphenamine Blood Dyscrasias, *Indian M Gaz* **73** 337, 1938.

186 Kadın, M. Aplastic Anemia Following the Use of Neoarsphenamine, *Arch Dermat & Syph* **37** 787 (May) 1938.

187 Briese, E. The Effect on the Blood Cells of the Fetal Rat Produced by the Inhalation of Carbon Tetrachloride by the Mother During Gestation, *Am J M Sc* **195** 787, 1938.

hemoglobin content, reticulocytosis, thrombocytosis, leukocytosis and an increased immaturity of the leukocytes, developed in the fetus

In the course of gold therapy in pulmonary tuberculosis, Daniello and Rusu¹⁸⁸ noted an increase in the hemoglobin content and in the eosinophil and lymphocyte counts. Some patients showed purpura, aggranulocytosis and anemia.

Shiraishi¹⁸⁹ found that yakriton (a fraction of liver not containing the principle potent against pernicious anemia) alleviated phenylhydrazine poisoning or the severe anemia which it causes in rabbits.

Loureau, de Sacy and Arthus¹⁹⁰ were able to produce a prolonged period of anemia in rabbits by the injection of lead salts three times a week for three weeks.

Ammonia, administered to rabbits, produced a reduction in the number of red blood cells and the hemoglobin content of the blood in the experiments of von Balo¹⁹¹. The anemia was proportional to the degree of poisoning. The cellular elements of the red bone marrow were destroyed first and later the myeloid (polynuclear) elements, with an increase in the number of lymphoid cells.

Kornblum, Boerner and Henderson¹⁹² studied before and after roentgen therapy certain features of the blood of 48 patients who did not have outstanding disease of the hemopoietic organs. After treatment, over half the patients showed a decrease in the red blood cell count and volume index, over 83 per cent showed a decrease in the leukocyte count, over 72 per cent showed a decrease in the number of neutrophils and in the platelet count, and over 81 per cent showed a decrease in the number of lymphocytes. The authors concluded that roentgen irradiation "depresses" the bone marrow and slows the production of cells. This, however, does not explain the fact that after irradiation many patients in their series showed just the opposite effect, namely, an increase in numbers. Yet they feel "no stimulating effects were observed". The authors¹⁹³ studied the blood of 100 patients with various types of cancer and lymphoblastoma treated with a wide range of doses of roentgen rays.

188 Daniello, L., and Rusu, V. *Hamatologische Veränderungen im Laufe der Goldtherapie*, Beitr z Klin d Tuberk **89** 352, 1937.

189 Shiraishi, S. *Studies on the Detoxicating Hormone of the Liver (Yakriton). Effect of Yakriton upon Phenylhydrazin Anemia in Animals of Low-Classed Liver Power*, Tohoku J Exper Med **32** 338, 1938.

190 Loureau, M., de Sacy, G. S., and Arthus, A. *Stabilité de l'anémie produite dans le saturnisme expérimental*, Compt rend Soc de biol **128** 512, 1938.

191 von Balo, J. *Der Einfluss der Ammoniakvergiftung auf das Blut und auf die Blutbildung*, Beitr z path Anat u z allg Path **101** 66, 1938.

192 Kornblum, K., Boerner, F., and Henderson, S. G. *The Qualitative Changes in the Formed Elements of the Blood Following Therapeutic Irradiation*, Am J Roentgenol **39** 601, 1938.

193 Kornblum, H., Boerner, F., and Henderson, S. G. *The Effects of Irradiation on the Normal Blood Cells as Determined by the Blood Count*, Am J Roentgenol **39** 235, 1938.

or radium. They concluded that with therapeutic doses there was no significant effect on the red blood cell count or the hemoglobin percentage and that anemia per se was not a contraindication to radium therapy. The greatest decrease occurs in the lymphocyte and then in the neutrophil count, while the monocyte and eosinophil counts are least affected. The part of the body treated and the dosage appeared to be minor factors compared with the size of the area treated. The leukocyte count usually returns to normal in five weeks, if it is prolonged to eight weeks the prognosis is unfavorable. Liver extract did not prevent the reduction in the leukocyte count or restore it to normal after treatment. Irradiation did not predispose to infection. "From a practical point of view," the authors concluded, "the effects of irradiation on normal blood, as determined by the blood count, are of little clinical significance." Furth, Tuggle and Breedis,¹⁹⁴ in experimenting with the action of x-rays on neoplastic cells, found that atypical cells of monoclear leukemia survived exposure to 5,000 roentgens but could not reproduce the disease after exposure to 15,000 roentgens. Virus diseases survive this dosage of roentgen rays, suggesting that neoplasms are not virus diseases. After irradiation, the cells do not die at once but reproduce for several generations (in vitro) before they degenerate and die. Yamashita¹⁹⁵ found a marked reduction in the number of leukocytes and lymphocytes in rats irradiated with neutrons, although the neutrophils were increased in number. Eosinophils disappeared quickly, the monocytes were first slightly increased in number and later slightly decreased. There was a slow decrease in the number of erythrocytes and in the hemoglobin content. Anemia was evident in all the organs, with a reduction in the size of the spleen, testis, ovary and bones.

In tumor-bearing animals, Clarkson, Mayneord and Parsons¹⁹⁶ noted profound anemia after irradiation. Iron deposits were found in the spleen, fatty changes were present in the liver and kidneys and the amount of lymphoid tissue was reduced.

Doan¹⁹⁷ found that during treatment with artificial fever, there was polymorphonuclear neutrophilia (newly delivered cells). There were destruction of lymphocytes and delayed monocytosis (younger forms). In induced pyrexia with malaria treatment or *Bacillus typhosus*, there is marked leukopenia during the chill. In typhoid pyrexia there is a

194 Furth, J., Tuggle, A., and Breedis, C. Quantitative Studies on the Effect of X-Rays on Neoplastic Cells, *Proc Soc Exper Biol & Med* **38** 490, 1938.

195 Yamashita, H. Experimentelle Untersuchungen über die biologischen Wirkungen der Neutronen, *Gann* **31** 654, 1937, abstracted, *Biological Effects of Deuteron-Deuteron-Neutrons*, *Nature*, London **141** 416, 1938.

196 Clarkson, J. R., Mayneord, W. V., and Parsons, L. D. The Effect of X-Radiation on the Blood and Lymphoid Tissue of Tumor Bearing Animals, *J Path & Bact* **46** 221, 1938.

197 Doan, C. A. Peripheral Blood Phenomena and Differential Response of Bone Marrow and Lymph Nodes to Hyperpyrexia, *Radiology* **30** 382, 1938.

temporary disappearance of the peripheral monocytes, but a moderate stimulation with typhoid vaccine and a marked stimulation from malaria treatment occur. In the latter type, clasmatocytes appear in the peripheral blood.

Bensley, Rhea and Mills¹⁹⁸ described the cases of a brother and sister with familial idiopathic methemoglobinemia. Only 5 cases had been recorded previously. Methemoglobin was identified spectroscopically, and the content of oxygen-carrying hemoglobin was less than the total hemoglobin content. No extraneous cause for the cyanosis was found.

Minot¹⁹⁹ has reviewed the effects of lead on the growth of plant and animal tissue, enzyme activity, formation of immune bodies, red blood cells, white blood cells, skeletal and smooth muscle and nervous and other systems.

THE BLOOD IN DISEASE OF THE KIDNEYS

Lowinger²⁰⁰ studied azotemic anemia (nephritis) by means of bone marrow puncture. The anemia is of the nonregenerative type, with inhibition of the maturation of the erythroblasts by a toxic substance.

Ishida²⁰¹ found that anemia followed glomerular injury with reagents but not when the tubules were damaged. The anemia-producing factor was insoluble in water, but it dissolved in lipid solvents and was saponifiable.

Drury²⁰² produced renal insufficiency in rabbits by limiting the blood flow in one kidney and later removing the other. Moderate anemia developed rapidly after the reduction of the total renal mass. Hemorrhage into the wall and lumen of the intestine was noted in many of the animals.

From roentgenograms of the bone marrow of patients with chronic nephritis, Nordenson²⁰³ concluded that there was a mild degree of aplasia of the precursors of red blood cells, without involvement of the white blood cells. The number of nucleated red blood cells was decreased.

198 Bensley, E. H., Rhea, L. J., and Mills, E. S. Familial Idiopathic Methaemoglobinaemia, *Quart J Med* **7** 325, 1938.

199 Minot, A. S. The Physiological Effects of Small Amounts of Lead. An Evaluation of the Lead Hazard of the Average Individual, *Physiol Rev* **18** 554, 1938.

200 Lowinger, S. Die Erythropoese bei azotamischen Anamien, *Folia haemat* **59** 222, 1938.

201 Ishida, K. A Supplement to "The Anemic Factor in Nephritis," *J Chosen M A* **27** 1506, 1937.

202 Drury, D. R. The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, *J Exper Med* **68** 693, 1938.

203 Nordenson, N. G. Bone Marrow in Anemia of Chronic Nephritis, *Folia haemat* **59** 1, 1938.

POLYCYTHEMIA

Haden ²⁰⁴ pointed out that whereas the total blood volume is constantly increased in polycythaemia vera, the plasma volume is seldom greater than normal. The red blood cell mass per kilogram is the most sensitive indicator of the changes in the red blood cells. The red blood cell mass is constantly high in polycythaemia vera but not significantly changed in symptomatic polycythemia. The total mass of red blood cells is a guide for the control of treatment.

Hallock ²⁰⁵ found that whereas in normal persons the average lactic acid concentration of the venous blood during rest was 13.9 mg per hundred centimeters and 16.3 mg after mild exercise, in polycythaemia vera the values were 17.8 and 15.1 mg, respectively. The same response to exercise, however, was found after reducing the red blood cell count and hemoglobin percentage to normal, suggesting that the disturbance of lactic acid metabolism in polycythaemia vera was dependent on some primary factor, to which the polycythemia itself was secondary. In the polycythemia of congenital heart disease the figures were 17.5 and 32.2 mg per hundred centimeters, respectively, and in marked emphysema the numbers were 19.8 and 22.2 mg.

Glasser ²⁰⁶ described the successful treatment of a 60 year old polycythemic woman with phenylhydrazine hydrochloride. Splenomegaly and hepatomegaly were unusually marked. Three of the patient's brothers and nephews had hemophilia.

Di Guglielmo ²⁰⁷ described acute erythremic myelosis (acute erythremia) as a clinical entity. It is characterized by severe anemia, irregular or remittent fever, splenomegaly, moderate hepatomegaly, the presence of basophilic erythroblasts in the blood, primary hyperplasia of the erythropoietic tissue, proliferation of the cells of the reticuloendothelial system, a duration of from one to two months and a fatal outcome. Incomplete and atypical forms are encountered. The disease occurs in both sexes and at all ages. Therapeutic efforts (liver, arsenic, an iron preparation or blood transfusions) are unavailing.

Rodes ²⁰⁸ found polycythemia (red blood cells, 7,540,000, hemoglobin, 118 per cent) in a 25 year old man with multiple hemangioma of the lung.

204 Haden, R. L. The Red Cell Mass in Polycythemia in Relation to Diagnosis and Treatment, *Am J M Sc* **196** 493, 1938.

205 Hallock, P. Blood Lactic Acid After Exercise, with Particular Reference to Polycythemia Rubra Vera, *Proc Soc Exper Biol & Med* **38** 587, 1938.

206 Glasser, S. M. A Case of Polycythemia Vera. The Familial Incidence of Hemophilia and Treatment with Phenylhydrazine, *J A M A* **110** 2071 (June 18) 1938.

207 di Guglielmo, G. L'érythremie aigue, *Rev belge sc méd* **10** 200, 1938.

208 Rodes, C. B. Cavernous Hemangiomas of the Lung with Secondary Polycythemia, *J A M A* **110** 1914 (June 4) 1938.

Clinically there were cyanosis of the lips, clubbing of the fingers and toes, jaundice, hemangiomas (small) of the lips and a history of hemoptysis. Death resulted from rupture of a hemangioma into the bronchus.

Stone and Woodman²⁰⁹ described a patient with polycythaemia vera in whom "leukoerythroblastic" anemia developed. The value for nucleated red blood cells in the peripheral blood rose to 84,000 and that of the white blood cells to 94,500 per cubic millimeter. Death resulted from cardiac failure. There was megakaryocytic hyperplasia of the upper two thirds of the femoral marrow with myelosclerosis below. Multiple foci of extramedullary hemopoiesis were found. Lymph glands showing caseous foci with acid-fast bacilli were present.

Cases illustrating the association of polycythemia and peptic ulcer were described by Sansone²¹⁰ and Schneiderbauer²¹¹.

Davis²¹² found that liver feeding reduced the polycythemia caused in dogs by exercise or cobalt chloride, in spite of the continuation of these agents. On cessation of the liver therapy, the polycythemia returned. Stomach U S P and liver extract by mouth were not effective, although one kind of liver extract given by daily intramuscular injections produced the same effect as whole liver in reducing the blood count. Major,²¹³ however, found that liver extract produced no specific effect when given to patients with polycythaemia vera.

Evesen²¹⁴ considers that the action of phenylhydrazine in polycythaemia vera is peripheral, the bone marrow being stimulated, not depressed. The same dosage may vary as to its effects on different patients. The first course of treatment should be given with the patient under hospital observation. In patients over 60 years of age the reaction is more rapid and severe, especially if arteriosclerotic or visceral disease is present.

McAlpin and Smith²¹⁵ analyzed the cases of 14 patients with polycythaemia vera treated with acetylphenylhydrazine. Of these, 9 were helped, 2 others, with peptic ulcer, were helped only temporarily. Three patients died. Two necropsies did not suggest toxicity of the drug, the

209 Stone, D. M., and Woodman, D. Polycythaemia Terminating in Leuko-Erythroblastic Anaemia, *J. Path. & Bact.* **47** 327, 1938.

210 Sansone, L. Osservazioni e considerazioni sulle poliglobulie, *Arch. per le sc. med.* **64** 451, 1937.

211 Schneiderbauer, A. Polycythaemia vera und Ulcus duodeni, *Ztschr. f. klin. Med.* **133** 474, 1938.

212 Davis, J. E. The Reduction of Experimental Polycythemia by Liver Administration, *Am. J. Physiol.* **122** 397, 1938.

213 Major, R. H. The Effect of Liver Extract on Polycythemia Vera, *J. Lab. & Clin. Med.* **24** 65, 1938.

214 Evesen, O. K. The Action of Phenylhydrazine in Polycythaemia Vera, *Acta med. Scandinav.* 1938, supp. 90, p. 288.

215 McAlpin, K. R., and Smith, K. E. Polycythemia Vera. Report of Fourteen Cases Treated with Acetylphenylhydrazine, *New York State J. Med.* **38** 101, 1938.

third patient probably had Ayerza's disease. One patient became jaundiced, and 2 showed a susceptibility to the drug in usual doses. The authors concluded that acetylphenylhydrazine is probably more effective and less toxic than phenylhydrazine hydrochloride.

Kandel and LeRoy²¹⁶ found that ascorbic acid had no influence on the red blood cell counts and hemoglobin levels of patients with polycythemia vera.

Sohval²¹⁷ described a case of polycythemia in which hepatic enlargement suddenly appeared and ascites and jaundice developed rapidly, owing to thrombosis of the hepatic veins. Hepatic enlargement was found to be moderate or marked in 30 of 60 cases of polycythemia. Marked enlargement of the spleen often indicated a complication, such as phenylhydrazine jaundice, leukemic transformation, myocardial decompensation, hepatic cirrhosis or thrombosis of the hepatic veins.

Rosenthal and Bassen²¹⁸ reviewed 13 cases of polycythemia, illustrating various courses and terminations. The blood picture may become leukemic, thrombocythemic or anemic or may show combinations of these phases.

PURPURA HAEMORRHAGICA

Bleeding may result from a decrease in the number of platelets, alterations in the plasma or changes in the permeability of the capillaries. The etiologic factors which produce these changes are manifold and have resulted in the description of various types of purpura. A clinical classification according to the complexities of the physiopathologic process and the multiple etiologic factors is of somewhat doubtful value.

Torrioli and Puddu²¹⁹ made extracts from spleens of patients with thrombopenic purpura. When this material was mixed with cultures of guinea pig bone marrow, marked injury to the megakaryocytes occurred. The authors were unable to identify this thrombopenic substance. They stated that it was also present in extracts made from a normal spleen, liver, lung, red muscle and lymphatic material but in lesser amounts. They were able to detect its presence in the blood of the splenic vein but not in that of the artery. Similar observations were made by Troland.

216 Kandel, E. V., and LeRoy, G. V. Note on the Lack of Hemoregulatory Effect of Ascorbic Acid on Patients with Polycythemia Vera, *Am J M Sc* **196** 392, 1938.

217 Sohval, A. R. Hepatic Complications in Polycythemia Vera, with Particular Reference to Thrombosis of the Hepatic and Portal Veins and Hepatic Cirrhosis, *Arch Int Med* **62** 925 (Dec.) 1938.

218 Rosenthal, N., and Bassen, F. A. Course of Polycythemia, *Arch Int Med* **62** 903 (Dec.) 1938.

219 Torrioli, M., and Puddu, V. Recent Studies on the Pathogenesis of Werlhof's Disease, *J A M A* **111** 1455 (Oct 15) 1938.

and Lee,²²⁰ with the exception that they could not identify or isolate this substance in extracts from normal or other types of diseased spleens

Purpura may be congenital or acquired Denninger²²¹ reported 2 cases of the fulminating type occurring in the same family From the information given, his conclusions are questionable Lymphoid hyperplasia associated with thrombopenic purpura was described by Cooley²²² Toxic purpura complicating scarlet fever was observed by Fox and Enzer²²³ A similar type of purpura was noted by Stoesser and Lockwood²²⁴ in varicella, and by Welt and Kasnetz²²⁵ in rubella Purpura resulting from drug poisoning may be due to a decrease in the platelet count or capillary injury Hill,²²⁶ Joekes,²²⁷ Moody²²⁸ and Hoffman, Kahn and Fitzgibbon²²⁹ all reported cases of purpura following the use of sedormid (allylisopropylacetylcarbamide) Allergic purpura due to sensitivity to the toxin of hemolytic streptococci was observed by Ellis²³⁰ Dutton²³¹ noted allergic purpura following the ingestion of citrus fruits Purpura due to benzene poisoning was noted by Keen¹⁸³

The symptoms associated with purpura are varied, depending on the location and severity of the hemorrhages, the cause of the condition, and

220 Troland, C E, and Lee, F C A Preliminary Report on a Platelet-Reducing Substance in the Spleen of Thrombocytopenic Purpura, Bull Johns Hopkins Hosp **62** 85, 1938, Thrombocytopenic A Substance in the Extract from the Spleen of Patients with Idiopathic Thrombocytopenic Purpura that Reduces the Number of Blood Platelets, J A M A **111** 221 (July 16) 1938

221 Denninger, H S Purpura Hemorrhagica Fulminans, Southwest Med **22** 8, 1938

222 Cooley, L E Lymphoid Hyperplasia Associated with Thrombopenic Purpura, Arch Path **26** 390 (July) 1938

223 Fox, M J, and Enzer, N A Consideration of the Phenomenon of Purpura Following Scarlet Fever, Am J M Sc **196** 321, 1938

224 Stoesser, A V, and Lockwood, W W Varicella Complicated with Acute Thrombocytopenic Purpura and Gangrene, J Pediat **12** 641, 1938

225 Welt, B, and Kasnetz, J Thrombopenic Purpura as a Complication Association with Acute Mastoiditis, Lateral Sinus Thrombosis, Streptococcus Viridans Bacteremia and Multiple Metastatic Abscesses, Arch Otolaryng **27** 732 (June) 1938

226 Hill, D B Thrombopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), J A M A **111** 1459 (Oct 15) 1938

227 Joekes, T Purpura Haemorrhagica (Werlhof) After Taking Sedormid, Lancet **2** 305, 1938

228 Moody, A M Thrombocytopenic Purpura Following Use of Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), J A M A **110** 726 (March 5) 1938

229 Hoffman, A M, Kahn, J, and Fitzgibbon, J P Thrombocytopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), J A M A **110** 725 (March 5) 1938

230 Ellis, R W B Allergic Purpura, Proc Roy Soc Med **31** 768, 1938

231 Dutton, L O Thrombopenic Purpura Due to Food Allergy Case Report, J A M A **111** 1920 (Nov 19) 1938

any existing disease which may be present Cook²³² commented on the complications arising from bleeding in persons who require dental care. The erythema crises of the visceral type of involvement have been emphasized by Poll²³³. This author pointed out that hemorrhage is more common in males, especially in adolescent and early adult life. An interesting observation was made by Abbott,²³⁴ who studied the course of infection in a case of purpura before and after splenectomy. Preceding the operation, the platelet count was decreased. After operation, in the presence of infection, the platelet count increased, as did the white blood cell count, and decreased as the infection subsided.

As the cause of purpura cannot be determined in every instance, treatment frequently results in failure. Further, since remissions are not uncommon, an evaluation of any therapeutic procedure is difficult. Doan²³⁵ recommended splenectomy in purpura with a platelet deficiency. Aitken²³⁶ observed a patient with thrombopenic purpura whose platelet count remained at a low level for at least one year after operation. Fleischhacker²³⁷ suggested the early use of kephrine hydrochloride (methyldaminoacetopyrocatechol hydrochloride) but recommended splenectomy for chronic purpura. Roentgen therapy has been employed by innumerable investigators. Jones, Tocantins and Smith²³⁸ believe it beneficial in certain selected cases of purpura. Garland²³⁹ suggested its use in various other hemorrhagic disorders, such as uterine bleeding, epistaxis, gastric oozing, chlorosis and melena neonatorum. Autohemotherapy has been successfully used by Saxon²⁴⁰. Imerman and Imerman²⁴¹ were able to control the hemorrhages in purpura by means of large doses of snake venom. The therapeutic effect of vitamin P has

232 Cook, T. J. Blood Dyscrasias from a Dental Point of View, *Am J Orthodontics* **24** 687, 1938.

233 Poll, D. Erythema Crises of the Visceral Group, *J Mt Sinai Hosp* **4** 997, 1938.

234 Abbott, K. H. Thrombocytopenic Purpura Hemorrhagica, *California & West Med* **48** 332, 1938.

235 Doan, C. A. Pathologic Physiology of the Spleen. Rationale of Splenectomy in Congenital Hemolytic Icterus, Thrombocytopenic Purpura and Early Banti's Disease, *Northwest Med* **37** 61, 1938.

236 Aitken, G. T. Review of a Case of Thrombocytopenic Purpura Treated by Splenectomy, *J Michigan M Soc* **37** 628, 1938.

237 Fleischhacker, H. Zur Therapie der thrombopenischen Purpura mit Stryphnon, *Wien klin Wchnschr* **51** 449, 1938.

238 Jones, H. W., Tocantins, L. M., and Smith, R. M. Splenic Irradiation in the Treatment of Purpura Hemorrhagica, *Ann Int Med* **11** 1311, 1938.

239 Garland, L. H. Roentgen Treatment of Certain Hemorrhagic Disorders. *California & West Med* **49** 123, 1938.

240 Saxon, L. Studies in Autohemotherapy. Report of a Case of Purpura Rheumatica with New Method of Treatment, *Illinois M J* **74** 191, 1938.

241 Imerman, C. P., and Imerman, S. W. Thrombocytopenic Purpura Hemorrhagica. Treatment with Massive Doses of Moccasin Snake Venom. *California & West Med* **48** 335, 1938.

been carefully studied by Jersild,²⁴² It is his opinion that the vitamin is specific in the Schonlein-Henoch purpuras

Since spontaneous cures are not uncommon, a conservative attitude must be adopted concerning the various therapeutic agents recommended Elliott²⁴³ pointed out that the suction test for capillary resistance in purpura is most helpful. Although it is not infallible, it appears to be a better index of bleeding than the platelet count and is affected earlier after splenectomy, thus serving as a valuable aid in determining the effect of treatment

HEMOPHILIA

Although hemophilia was recognized in early biblical times, Otto, in 1803, was the first accurately to describe this disease. The essential characteristics are its inheritance, the occurrence in males, transmission by females, a history of repeated hemorrhages, a prolonged clotting time and a normal bleeding time. Riddell and Haldane²⁴⁴ have emphasized the importance of the hereditary aspect of the disease. The familial incidence of hemophilia has also been stressed by Glasser²⁴⁵

Because of the disturbance in the clotting mechanism of the blood, complications due to hemorrhages are extremely common. It was previously pointed out that about 78 per cent of hemophiliacs have orthopedic complications and approximately 60 per cent have permanent deformities. A case of hemophilia with a fatal spontaneous hemorrhage from a pharyngeal abscess has been reported by Laurent²⁴⁶. The seriousness of abnormal bleeding as a surgical risk has been reviewed by Mertz and Meiks²⁴⁶. These authors cited a case of fatal nephrectomy in which the bleeding could not be controlled by transfusions or any other known methods. It is the impression of these investigators that the clotting time cannot be a satisfactory criterion of the clinical course.

There is no known specific therapy. Clark and his co-workers²⁴⁷ described a preparation made from egg white which has proved satisfactory in reducing the clotting time when given parenterally. Pohle

242 Jersild, T. Therapeutic Effect of Vitamin P in Schonlein-Henoch Purpura, *Lancet* **1** 1445, 1938

243 Elliott, R. H. E. The Suction Test for Capillary Resistance in Thrombocytopenic Purpura, *J. A. M. A.* **110** 1177 (April 9) 1938

244 Riddell, W. J. B., and Haldane, J. B. S. A Haemophilic and Colour-Blind Pedigree, *J. Genetics* **36** 45, 1938

245 Laurent, L. J. M. Haemophilia with Fatal Spontaneous Haemorrhage from Pharyngeal Abscess, *Brit. J. Child Dis.* **34** 282, 1937

246 Mertz, H. O., and Meiks, L. T. The Hemophiliac as a Surgical Risk. Report of a Case of Nephrectomy with Death, *Urol. & Cutan. Rev.* **42** 557, 1938

247 Clark, G. A., Gaunt, R. T., and Timperley, W. A. Some Observations on Blood Clotting, *Quart. J. Exper. Physiol.* **28** 149, 1938

and Taylor ²⁴⁸ have demonstrated that a globulin substance derived from beef plasma is most effective in controlling hemorrhages in hemophiliacs when applied locally. However, it is of little value when taken orally. These same authors ²⁴⁹ have also shown that normal or lyophilized plasma contains some unknown substance which aids in the reduction of the clotting time. The factor is not present in globulin. Lawson and Graybeal ²⁵⁰ recommended frequent venesection to reduce the bleeding tendency in hemophiliacs, as it is their opinion that increased venous pressure and damaged capillaries may be contributing factors to the hemorrhage.

BLOOD CLOTTING

The various theories concerned with clot formation have been reviewed by Magath, ²⁵¹ who also stressed the importance of the role of vitamin K in the development of a blood clot and its relation to prothrombin. The historical development, research problems and chemistry of vitamins K and P have been summarized by McCay ²⁵². The best sources of vitamin K, as pointed out by Osterberg, ²⁵³ are hog liver oil, cabbage, spinach, tomatoes and alfalfa. Dam and Glavind ²⁵⁴ have investigated the vitamin K content of various plants by the curative technique. The richest sources are green leaves, chestnut leaves being the most potent. The strength of the vitamin was only slightly altered when the leaves were withering, and the vitamin was equally distributed throughout the leaves, especially in those with alternating yellow and green areas. Flowers, roots and seeds were poor sources. The lower plants had considerably less vitamin K than the higher plants. Germination in the light enabled peas to synthesize a considerable amount of the vitamin, but the same plant synthesized only a limited amount in the dark.

248 Pohle, F. J., and Taylor, F. H. L. The Use of a Globulin Substance Derived from Beef Plasma as a Local Hemostatic in Hemophilia, *J. Clin. Investigation* **17** 677, 1938.

249 Pohle, F. J., and Taylor, F. H. L. The Coagulation Defect in Hemophilia. Studies on the Refractory Phase Following Repeated Injections of Globulin Substance Derived from Normal Human Plasma in Hemophilia, *J. Clin. Investigation* **17** 779, 1938.

250 Lawson, G. B., and Graybeal, A. B. Hemophilia Treated by Venesection, *J. A. M. A.* **111** 2104 (Dec. 3) 1938.

251 Magath, T. B. Coagulation of Blood with Special Reference to Prothrombin, *Proc. Staff Meet., Mayo Clin.* **13** 67, 1938.

252 McCay, C. M. Other Factors—Less Well Known Vitamins, *J. A. M. A.* **110** 1441 (April 30) 1938.

253 Osterberg, A. E. Vitamin K—Its Distribution and Chemical Properties. Methods of Preparation and Assay, *Proc. Staff Meet., Mayo Clin.* **13** 72, 1938.

254 Dam, H., and Glavind, J. Vitamin K in the Plant, *Biochem. J.* **32** 485, 1938.

Almquist and his co-workers²⁵⁵ were able to demonstrate the presence of vitamin K by assay methods in materials acted on by various bacteria. They suggested that the vitamin was a product of bacterial metabolism.

As pointed out by Osterberg, vitamin K is fat soluble, and non-nitrogenous, has an aromatic nucleus, but contains no phosphorus or sulfur. It has no sterol ring and is alkali labile, heat stable and optically inactive, with a molecular weight of 600.

An accurate method of estimating the prothrombin level and of determining the role of prothrombin in clot formation has been described by Quick.²⁵⁶ This investigator frequently has demonstrated the production of hemorrhagic disease in chicks on diets deficient in vitamin K, the bleeding is apparently related to a prothrombin deficiency and occurs when the level of prothrombin is less than 20 per cent of normal. In human beings, bleeding usually occurs when there is a 90 per cent deficiency or more. Prothrombin deficiency may be produced not only by a deficient intake of vitamin K, as pointed out by Quick, but also by hepatic damage, failure of absorption and a direct toxic effect, as seen in sweet clover disease. Thayer and his colleagues,²⁵⁷ as well as Ansbacher,²⁵⁸ have also demonstrated the presence of a hemorrhagic tendency in chicks on deficient diets. They have been able to alleviate the bleeding by giving vitamin K. Ansbacher has recommended this method of assaying the potency of the product. Both the amount of material necessary and the duration of the therapeutic effect of the vitamin may be accurately determined.

A bleeding tendency and a prothrombin deficiency have been produced in dogs with biliary fistulas by Smith and his collaborators.²⁵⁹ These authors conclusively demonstrated the failure of absorption of vitamin K when bile was absent from the gastrointestinal tract. The addition of bile to the normal diet restored the lowered prothrombin level to normal. The addition of vitamin K alone to the diet was of little value, as was also true of vitamins A and D. Similar clinical observations were

255 Almquist, H. J., Pentler, C. F., and Mecchi, E. Synthesis of the Anti-hemorrhagic Vitamin by Bacteria, *Proc. Soc. Exper. Biol. & Med.* **38** 336, 1938.

256 Quick, A. J. The Nature of the Bleeding in Jaundice, *J. A. M. A.* **110** 1658 (May 14) 1938.

257 Thayer, S. A., McKee, R. W., MacCorquodale, D. W., and Doisy, E. A. Recovery from the Anemia Caused by a Diet Deficient in Vitamin K, *Proc. Soc. Exper. Biol. & Med.* **37** 417, 1937.

258 Ansbacher, S. New Observations on the Vitamin K Deficiency of the Chick, *Science* **88** 221, 1938.

259 Smith, H. P., Warner, E. D., Brinkhous, K. M., and Seegers, W. H. Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs. Effect of Feeding Bile and Vitamin K, *J. Exper. Med.* **67** 911, 1938.

reported by Snell,²⁶⁰ Butt, Snell and Osterberg,²⁶¹ and Warner, Brinkhous and Smith²⁶² for patients with obstructive jaundice. Those with a bleeding tendency associated with obstructive jaundice had a markedly reduced prothrombin level, which could be restored to normal by the addition of bile alone to the diet, or bile plus vitamin K, with the subsequent elimination of the hemorrhages. Dam and Glavind²⁶³ stated that thrombopenia, aplastic anemia, hemophilia, nontropical sprue, myeloma, acute hepatitis, obstructive jaundice, cholelithiasis and carcinoma have a definite influence on the clotting time. It is their impression also that the bleeding tendency is a result of vitamin K deficiency, with an associated decrease in the prothrombin level.

Ferguson²⁶⁴ stressed the importance of the quantitative relations of calcium and cephalin in thrombin formation. By means of a carefully standardized and controlled technic the author has demonstrated that calcium is a more fundamental determinant of the thrombin formation and that cephalin has a secondary influence up to a certain point in increasing the thrombin formation. Quick²⁶⁵ has pointed out that antithrombin is an albumin or a substance closely associated with this fraction. Heparin is not antithrombin, but because of its affinity for the albumin, it intensifies the inherent antithrombic activity of this material. MacFarlane²⁶⁶ has reported a case of fibrinopenia in a young boy with an associated bleeding tendency.

The role of the blood platelets in hookworm anemia has been studied by Landsberg²⁶⁷. He produced the disease by infecting dogs, but regard-

260 Snell, A. M. Symposium on Hemorrhagic Diathesis in Cases of Jaundice. Its Relation to Vitamin K Deficiency, Preliminary Report, Clinical and Experimental Conditions Associated with Deficiency of Prothrombin, Proc. Staff Meet., Mayo Clin **13** 65, 1938.

261 Butt, H. R., Snell, A. M., and Osterberg, A. E. The Use of Vitamin K and Bile in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, Proc. Staff Meet., Mayo Clin **13** 74, 1938. Snell, A. M., Butt, H. R., and Osterberg, A. E. Treatment of the Hemorrhagic Tendency in Jaundice, with Special Reference to Vitamin K, Am. J. Digest. Dis. **5** 590, 1938.

262 Warner, E. D., Brinkhous, K. M., and Smith, H. P. Bleeding Tendency of Obstructive Jaundice. Prothrombin Deficiency and Dietary Factors, Proc. Soc. Exper. Biol. & Med. **37** 628, 1938. Brinkhous, K. M., Smith, H. P., and Warner, E. D. Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula. Effect of Feeding Bile and Alfalfa (Vitamin K), Am. J. M. Sc. **196** 50, 1938.

263 Dam, H., and Glavind, J. Vitamin K in Human Pathology, Lancet **1** 720, 1938.

264 Ferguson, J. H. Quantitative Relationships of Calcium and Cephalin in Experimental Thrombin Formation, Am. J. Physiol. **123** 341, 1938.

265 Quick, A. J. The Normal Antithrombin of Blood and Its Relation to Heparin, Am. J. Physiol. **123** 712, 1938.

266 MacFarlane, R. G. A Boy with No Fibrinogen, Lancet **1** 309, 1938.

267 Landsberg, J. W. The Blood Platelets in Hookworm Anemia, Am. J. Hyg. **27** 316, 1938.

less of whether or not the disease was fatal, there were no alterations in the circulating platelets or any noticeable toxic effect on the bone marrow

BANTI'S DISEASE

Since 1881, when Banti described the disease which bears his name, sufficient evidence has accumulated to question the existence of this syndrome. Banti postulated that an unidentified toxic agent is the etiologic factor and that this substance is carried to the spleen, with secondary involvement of the liver. Sclerosis of the splenic vessels, atrophy of the malpighian corpuscles, induration of the pulp, sclerosis of the portal system and atrophic cirrhosis of the liver were the pathologic changes observed. Splenectomy effects a cure.

Menon²⁶⁸ produced splenomegaly in rats and rabbits by narrowing the lumen of the portal vein for various lengths of time. The splenic sinuses appeared dilated, and there were distention of the pulp and trabecular veins, variable atrophy of the pulp and only a slight fibrillary increase. Hyperplastic reactions were absent. Complete obstruction of the portal vein was invariably fatal to the rats in three to forty-eight hours and to the rabbits in twenty to ninety-six hours. He concluded that portal obstruction is probably not the cause of Banti's disease. However, Hines and Fitzgerald²⁶⁹ offered evidence from the autopsy study of a patient with so-called Banti's disease showing that the maintenance of hypertension in the sclerotic portal system is the etiologic factor in the production of the pathologic changes characteristic of hepatolienal cirrhosis.

Kemp²⁷⁰ and Howells²⁷¹ have reviewed reports of large series of cases of Banti's disease. The outstanding symptoms and signs, in the order of their frequency, are splenomegaly, weakness, hemorrhage, enlargement of the liver, jaundice and ascites. The anemia present may be microcytic or macrocytic. The former is undoubtedly due to acute or chronic hemorrhage. Howells divided his cases into three groups according to the severity of the anemia and stated that approximately 81 per cent of the patients with severe anemia had hematemesis, whereas in the group with slight anemia, no hemorrhage was observed. The macrocytic anemia is probably due to the interference of erythropoiesis as a result of failure of the abnormal liver to store or present for

268 Menon, T. B. Venous Splenomegaly. A Study in Experimental Portal Congestion, *J. Path. & Bact.* **46** 357, 1938.

269 Hines, L. E., and Fitzgerald, B. Splenomegaly of the Banti type. Report of a Case with Postmortem Observations Four Years After Splenectomy. *Arch. Path.* **26** 155 (July) 1938.

270 Kemp, R. Recurrent Haematemesis in "Banti's Disease," *Brit. M. J.* **1** 222, 1938.

271 Howells, L. Treatment of Splenic Anaemia and Banti's Syndrome, *Lancet* **1** 1320, 1938.

utilization to the bone marrow the substance necessary for the maturation of red blood cells

Although there is considerable disagreement as to the existence of this disease, Rubnitz,²⁷² Alessandri²⁷³ and De Candia and Floriani²⁷⁴ stressed the importance of an accurate diagnosis in governing the selection of proper treatment. De Candia and Floriani suggested the intramuscular use of thymic extract as a method to differentiate the splenomegalies. They could produce an increase in the number of red blood cells, leukocytosis and splenic contraction in normal persons, as well as those with malaria, by intramuscular injections of thymic extract, but no changes were observed in patients with Banti's disease, hence, the suggestion that this test could be employed as a diagnostic procedure.

Splenectomy has long been considered the accepted treatment for this type of splenomegaly. A résumé of the early literature is misleading, as many of the reported cases were not cases of Banti's disease. Further, the disease may run a protracted course, so that any conclusions concerning the benefits derived from splenectomy must be guarded. Alessandri stated that removal of the spleen is indicated if portal thrombosis is not present. Dods²⁷⁵ believes that operation is to be recommended only in the early course of the disease but is not enthusiastic about the results. Kemp²⁷⁰ has suggested ligation of the varices as well as splenectomy or ligation of the splenic artery. Howells²⁷¹ is of the opinion that splenectomy does not affect the disease process. Iron may or may not be of value in eliminating the anemia. In his series, patients treated conservatively on a medical regimen lived as long as or longer than those with the spleen removed. He has suggested that the apparent difference in the life span of those operated on and of those not operated on may be due to the high mortality rate associated with the surgical procedure.

INFECTIOUS MONONUCLEOSIS

In a most comprehensive review Tidy²⁷⁶ has summarized the various features relative to glandular fever and infectious mononucleosis. The disease was first described by Filatow, in 1885. Pfeiffer, in 1889, Desplats and Horschelmann, in 1894, Sprunt and Evans, in 1920, Lancopé, in 1920, and Downey and McKinley, in 1923, have all made important contributions relative to this disease.

272 Rubnitz, A. S. Blood Changes Associated with Different Splenomegalies, *Nebraska M J* **23** 87, 1938.

273 Alessandri, R. Experiences with Surgery of the Spleen. Report of Two Unusual Cases, *J Mt Sinai Hosp* **4** 489, 1938.

274 de Candia, S., and Floriani, F. Azione del timo sull'emopoiesi e sulla milza, *Polichimico (sez prat)* **45** 1553, 1938.

275 Dods, L. Indications for Splenectomy in Paediatric Practice, *M J Australia* **1** 377, 1938.

276 Tidy, H. L. Glandular Fever and Infectious Mononucleosis, *St Thomas's Hosp Rep* **2** 104, 1937.

As pointed out by Tidy, various organisms have been isolated and described as the etiologic factor of infectious mononucleosis, but none of them has ever been confirmed by any one other than the original investigator. The disease has occurred in various parts of the world in sporadic or epidemic form. Persons of either sex or of any age may be afflicted with glandular fever, though it is much more common in persons under 40, especially children.

The clinical course of the disease, as emphasized by Blum,²⁷⁷ may be divided into three types: glandular, involving the lymphoid tissue in the cervical, axillary and inguinal regions; angiose, in which the symptoms involving the throat are outstanding; and the febrile type, which is most difficult to diagnose. The most common symptoms, as described by various clinicians, are general malaise, headache, tenderness of the glands, sore throat, chilliness, backache, coryza, anorexia, sweating, weakness, cough, dizziness, soreness and bleeding of the gums, nausea, stiff neck, epistaxis, stomatitis, abdominal pain, rash, photophobia and conjunctivitis. Tribble²⁷⁸ commented on the oral lesions occurring in the various blood dyscrasias. It is his opinion that infection is the primary cause and that the resulting blood picture enhances the condition. Beliveau and Russell²⁷⁹ described a case of infectious mononucleosis in a 19 year old girl in whom the outstanding symptoms were similar to those of acute appendicitis. These authors also emphasized the symptoms related to the throat and stated that they may occur late in the course of the malady.

The more common physical signs are fever, enlargement and tenderness of the glands, injection and ulceration of the mouth and throat, enlargement of the spleen, hypertrophy of the tonsils and a maculopapular rash. Although enlarged glands are present in practically all cases and tenderness in more than half, suppuration of the glands is most rare.

The prognosis is excellent. The disease is apparently self limited, with relapses and remissions not uncommon. Often the course may be protracted, and both glandular and hemopoietic changes may be present for months.

The diagnosis usually can be made by the characteristic clinical and laboratory features. Leukocytosis of varying degree is present at some time during the course, leukopenia may be observed at the onset. There is present in increased numbers an atypical mononuclear cell, which is generally considered to be a lymphocyte, though all investigators will

277 Blum, L. L. Infectious Mononucleosis, *J. Indiana M. A.* **31** 296, 1938.

278 Tribble, G. B. Clinical Manifestations in the Nose, Throat and Sinuses in Diseases of the Mononucleosis Type, *Tr. Am. Acad. Ophth.* **42** 367, 1937.

279 Beliveau, R. A., and Russell, B. W. Infectious Mononucleosis (Glandular Fever). Report of a Case Presenting Symptoms of Acute Appendicitis, *Maine M. J.* **29** 167, 1938.

not concur with this opinion. The heterophile antibody test (Paul and Bunnell) appears to be practically specific for glandular fever (serum sickness to be excluded). Davidsohn²⁸⁰ has again confirmed the value of this procedure and has devised a presumptive test which he believes will be of greatest value in borderline cases. The nature of the antibodies in infectious mononucleosis has received considerable attention. Bernstein²⁸¹ and Hatz²⁸² have called attention to the falsely positive reaction to the Wassermann test and its occurrence in this disease. These authors are of the opinion that the antibodies for these tests are not the same. Davidsohn²⁸³ studied the isoagglutinins in various leukopoietic disorders and observed that the titers in infectious mononucleosis are within the normal range.

Since the disease is self limited and the cause unknown, no specific treatment has been devised. Rest in bed, forcing of fluids, a high caloric diet and any other necessary palliative measures are indicated.

GRANULOCYTOPENIA

Since the widespread recognition of granulocytopenia, following the clinical description of the syndrome by Schultz in 1922, many articles concerning its etiology, pathology, prognosis and treatment have appeared. Reports relating to the disease during the past year have been concerned chiefly with three of its aspects, as follows: the etiologic significance of certain drugs, especially sulfanilamide, the apparent decreasing incidence of the disease, and the evaluation of various types of therapy.

An excellent summary of contemporary knowledge concerning the neutropenic states has been given by Kracke²⁸⁴. He considers that until recently leukopenia has been regarded as secondary because it is usually in association with some other disease. The conditions which are stated to be characterized by neutropenia are measles, German measles, mumps, influenza of the respiratory tract, chronic malaria, Brucellosis, typhus fever, typhoid and overwhelming infectious processes due to pyogenic organisms. Furthermore, neutropenia is frequently observed in Banti's disease, some of the lymphogranulomas, glandular tuberculosis and many conditions in which the bone marrow is directly involved, such as

280 Davidsohn, I. Test for Infectious Mononucleosis, *Am J Clin Path (Tech Supp)* **2** 56, 1938.

281 Bernstein, A. False-Positive Wassermann Reactions in Infectious Mononucleosis, *Am J M Sc* **196** 79, 1938.

282 Hatz, B. Wassermann Reaction in Infectious Mononucleosis, with Report of a Case with Unusual Clinical Features, *Am J Clin Path* **8** 39, 1938.

283 Davidsohn, I. Isoagglutinin Titers in Serum Disease, in Leukemias, in Infectious Mononucleosis, and After Blood Transfusions, *Am J Clin Path* **8** 179, 1938.

284 Kracke, R. R. The Neutropenic Diseases, *Bull New York Acad Med* **14** 725, 1938.

multiple myeloma, miliary tuberculosis and bone marrow carcinomatosis. Although it is stated frequently that secondary neutropenic states are brought about by the action of bacteria or their toxins, he considers that there is scant proof available in support of this. He is quite ready to admit, however, that in some cases there is an infectious factor. The explanation of the neutropenia in some of the infectious diseases, he believes, is that the available circulating leukocytes are drawn to the site of the infection in order to combat it. Benzene, gasoline fumes, excessive radiation from radium, roentgen rays and sunlight, dietary deficiency and adrenal insufficiency are also mentioned as causes of neutropenia.

A more extensive discussion has been given by Kracke of the etiologic significance of the pain-relieving drugs, especially aminopyrine, in relation to the syndrome of granulocytopenia. Although there are a number of reasons for considering that this substance is the cause of the syndrome in many cases, he considers that definite proof has come from two lines of research. The most conclusive of these is that neutropenia can be reproduced by the administration of as little as a single dose to a susceptible person. The other is the complete disappearance of the disorder from Denmark when the use of aminopyrine was forbidden by governmental decree. It is his opinion that arsphenamine, in addition to causing aplastic anemia, may be responsible likewise for granulocytopenia, in which the involvement of the marrow is limited exclusively to depression of the granulocytes. He likewise believes that dimtrophenol can produce marked leukopenia, but as the other severe untoward effects of the drug are now recognized, it is rarely used and is therefore of little importance in the causation of granulocytopenia.

Sulfanilamide, in the opinion of Kracke, can cause granulocytopenia and, with the increasing use of this drug, it is predicted that an increasing number of cases will be encountered. He was able to collect reports of 14 cases of the syndrome following its use. Usually leukopenia followed the administration of large doses over a considerable period. He was unable to discover instances in which the syndrome followed the administration of relatively small quantities of the drug, which led him to believe that the leukopoietic depression differs from that produced by aminopyrine. It is thought that sulfanilamide can at times cause increased activity of the leukopoietic centers which results in an extremely high leukocyte count, but no explanation has been offered for this apparent stimulation. In our opinion the occurrence of striking leukocytosis in a patient with an infection, especially a child, who receives the drug may be due entirely to the normal response of the bone marrow to the infection.

In the aforementioned article a discussion of the mechanism of the production of the disease has been included. It is believed that the initial change is cessation of cellular output, although we think that a better term would be reduction rather than cessation, this results in a decrease

in the number of granulocytes in the circulating blood which may precede the appearance of symptoms by several days. The mechanism by which the offending agent operates to depress the marrow function is not known, but, regardless of the cause, it is considered that there is frequently an arrest of maturation, as first suggested by Fitz-Hugh and Krumbhaar. The clinical symptoms are coincident with bacterial invasion.

Two important diagnostic points are emphasized by Kracke. The first is that the patient with granulocytopenia seldom shows any disturbance of the hemoglobin, red blood cells or platelets of the circulating blood unless the process is prolonged. It is made clear, however, that there is no reason why a patient with granulocytopenia should not have associated anemia. This is especially true of those who have previously been suffering from other diseases. We should like to insist, however, that the presence of severe associated anemia often casts considerable doubt on the diagnosis of true granulocytopenia. A second point about which there appears to be general agreement is that these patients may exhibit a marked degree of prostration which seems entirely out of proportion to the physical signs. In some instances, the physical examination may yield no other information except evidence of fever and prostration. In our opinion, it is also true that there may be definite leukopenia at a time when few, if any, symptoms are present.

Kracke regards the present method of treatment as highly unsatisfactory and considers that "no one man probably has treated a sufficient number of cases to form a proper evaluation of therapeutic agents." He has pointed out that a patient with granulocytopenia is suffering from two distinct diseases, "not only is the patient depleted of granulocytes, but in addition to this, often times has become overwhelmed with invading organisms." On the basis that granulocytopenia is an emergency illness and that the use of any therapeutic agent of even possible value is justifiable, it is his practice to give repeated blood transfusions, liver extract in "ten times the ordinary dosage by injection," pentnucleotide, yellow bone marrow by mouth and symptomatic therapy. Even with the use of these, he has admitted that the mortality rate in his recent cases very closely approximated that of the earlier years. We are not entirely in agreement with these conclusions regarding therapy. In the first place, owing to the decreasing incidence of granulocytopenia, it has not been possible to evaluate the newer therapeutic agents properly. Secondly, the mortality rate for those patients who have been treated symptomatically and who, it can positively be stated, have not been given aminopyrine in some form or another during the acute illness, is not known. We are in accord with his statement that much more can be done by preventing the syndrome than by treatment after it has once developed.

In a second comprehensive article Kracke²⁸⁵ has evaluated the data accumulated since 1931 which deal with the etiologic relation of certain drugs to granulocytopenia. The evidence is summarized regarding the etiologic significance of aminopyrine, arsphenamine, dinitrophenol and sulfanilamide. It is considered that conclusive proof is available which indicates that the disease may be caused by aminopyrine. This occurs only in an occasional person of the many who take the drug. Furthermore, it appears reasonable to conclude that the disease appears only in those who are allergic or sensitive to aminopyrine, therefore, the quantity which is administered bears little relation to the production of the disease. Incriminating information which points to the etiologic role of the substance is as follows. First, the disease occurs most frequently in those parts of the world where aminopyrine has the greatest use. Studies of the sharply declining incidence in Denmark, where the drug is now prohibited by law, are especially convincing. Second, its occurrence is greatest among those persons in any given vicinity who are the greatest users of aminopyrine. Third, a large majority of patients who have granulocytopenia are known to have taken the drug a short time prior to the onset of the condition. Fourth, and this is the most convincing evidence, the administration of the drug to patients who have recovered from the disease is followed by a reduction in the number of polymorphonuclear leukocytes in the peripheral blood. It has been emphasized that granulocytopenia may follow the use of a drug closely allied to aminopyrine, which is marketed under the name of novaldin (sodium phenyldimethylpyrazolon methylaminomethane sulfonate). It has the same chemical formula except that one of the methyl groups attached to the amino nitrogen is replaced by the sodium salt of methyl-sulfonic acid. The etiologic significance of this preparation has been demonstrated by the occurrence of leukopenia after its administration to a patient who had suffered previously from an attack of granulocytopenia induced by aminopyrine. It has been mentioned that antipyrine, which is the chemical precursor of and closely related to aminopyrine, has been suspected of producing the disease, but it appears to us that convincing evidence in this regard is lacking.

Kracke stated that the frequency of the disease in the southeastern part of the United States has decreased, as "the condition is now rarely seen," and concluded that this is also true throughout the country. He cited information, however, supplied by the United States Bureau of Vital Statistics for the years 1931 to 1936, inclusive, which indicates that there has been little change in the occurrence of the disease, as recorded in the mortality statistics, during these six years. These data should be accepted with the reservation, however, that errors of diagnosis might make them inexact. It is not inconceivable that other disorders,

285 Kracke, R. R. Relation of Drug Therapy to Neutropenic States, *J. A. M. A.* **111** 1255 (Oct 1) 1938.

such as aplastic anemia or overwhelming sepsis, might be regarded incorrectly as true granulocytopenia. On the other hand, improved methods of diagnosis might lead to the discovery of more cases, and as a result of a better understanding of the condition, it is possible that recovery occurs more commonly than in previous years. In our opinion, there has been a decrease in the incidence of the disease in recent years throughout the United States. There is no convincing information available, however, which indicates conclusively that this is due to the less frequent use of aminopyrine or allied substances either alone or in combination with other drugs. It can be suspected that this is the case because reliable data exist which indicate that the decrease of the incidence of the disease in Denmark paralleled the less frequent use of the drug.

It is contemplated by Kracke that granulocytopenia will continue to follow the administration of aminopyrine for two reasons. First, an occasional physician will continue to prescribe it, second, it will be used unknowingly in combinations with other pharmacologic agents. Physicians are advised to refrain from the use of aminopyrine or analgesic agents that contain it, and patients should be warned against the dangers of self medication, particularly the purchase and use of pain-relieving remedies for which the formulas are not available. In general, we consider that this advice is sound, but certainly in one disease, acute rheumatic fever, it is the drug of choice for those who cannot tolerate the salicylates. The judicious use of aminopyrine in this condition cannot be condemned.

Other drugs which have been reported as possibly causing granulocytopenia have been discussed by Kracke. He concluded that arsphenamine, dinitrophenol and sulfanilamide are also unquestionably capable of producing the disease. Others which have been suspected by various writers are novaldin (a derivative of aminopyrine), antipyrine, acetophenetidin, acetanilid, cinchophen, neostibosan (an antimony compound), quinine and gold salts. A fairly complete list of the trade names of various preparations containing aminopyrine has been recorded in his article and should be useful to every physician.

It is entirely possible that all the drugs mentioned by Kracke and perhaps others as yet unrecognized are capable of producing the syndrome of granulocytopenia. Before accepting the etiologic relation of any given drug to the disease, however, the following points must be considered. First, has it been demonstrated that the drug can produce definite leukopenia in a patient who has recovered from the disease which it is alleged to have caused? Second, is there reasonable proof that other recognized leukocyte-depressing drugs have not been taken? Third, can it be established that the leukopenia is a true granulocytopenia and not due to sepsis or associated with some other blood dyscrasia? Until

these criteria have been satisfied, the evidence in regard to any given drug cannot be regarded as unequivocal

Kracke has referred to the review by Plum and the report by Blew dealing with the etiologic relation between arsphenamine, with and without associated bismuth therapy, and granulocytopenia. In this summary 14 cases are reported in which the hematologic defect was limited to granulocytopenia, and there was no anemia or hemorrhagic diathesis. Other reports confirm this. It has long been known that arsenic compounds can produce aplastic anemia, but it is important to establish that they can also cause true granulocytopenia. The evidence is suggestive but not conclusive that this is the case.

Kracke has summarized the data regarding 11 cases of granulocytopenia following the administration of sulfanilamide which have been reported since April 1937 and has added 2 of his own. Death occurred in 10 of the 13 cases. In his opinion, this drug should be added to those which are capable of producing the disease. As the syndrome usually developed after the administration of large amounts of the drug (40 to 50 Gm.), he has reemphasized that the mechanism of granulopoietic depression may be different from that following the administration of a single dose of aminopyrine. We wish to stress, however, that unless an idiosyncrasy exists, it is difficult to understand why in only a very rare patient among the many thousands who have received this drug in the past few years the condition develops.

Fitz-Hugh²⁸⁶ stated that agranulocytic angina or, as he called it, pernicious leukopenia is now almost universally believed to be caused by an acquired sensitivity of the leukocytes, endothelium and leukopoietic tissues to certain drugs and other allergens (or potential toxins). He regards sensitivity, hypersensitivity and allergy as synonymous terms and, along with the expression idiosyncrasy, as meaning drug allergy. When the latter term is used, he considers that there has been a prior specific sensitizing contact, probably acting through a drug-protein combination, which is followed by an allergic response on repetition of contact with the drug. This reaction may be precipitated by a minute dose of the substance, and it does not necessarily resemble the usual pharmacologic or toxic action of the drug. He listed the drugs which have been suspected or proved to be the allergic cause of granulocytopenia as follows: "aminopyrine, dinitrophenol, arsphenamine and neoarsphenamine, gold salts, the diethylamine salt of stibanilic acid (neostibosan), acetophenetidin, sodium phenyldimethyl pyrazolon methylaminomethane sulfonate (novaldin), a preparation containing about equal molecular parts of aminopyrine and 8-hydroxyquinoline-5-sulfonic acid [causalin], quinine, cinchophen, bismuth, 5-phenyl-5-ethyl-

²⁸⁶ Fitz-Hugh, T, Jr. Sensitivity Reactions of the Blood and Bone Marrow to Certain Drugs, *J A M A* **111** 1643 (Oct 29) 1938

hydantoin (mirvanol), plasmoquine 8-dimethylamino-iso-amyl 6 methoxyquinoline (plasmochin) and sulfanilamide." Other causes which Fitz-Hugh would classify as "possible conditioning factors" in drug allergy are as follows: endocrine disturbances, bacterial sensitization, cyclic toxemia, fatigue states, accidental and surgical trauma, genetic predisposition and vitamin deficiency. It is obvious that such an amazing group of possibilities can mean only that these conditioning factors, if they are of importance, have not been established on a firm scientific foundation.

It is emphasized again by this author that the mechanism leading to agranulocytosis is to be found in the arrest of maturation of the leukocytes in the bone marrow. We believe that this is the most acceptable idea of the pathologic change in the disease. We see no reason, however, why the phenomenon of "sticking" of leukocytes to vascular endothelium should be postulated to explain the sudden temporary disappearance of granulocytes from the circulation (granulocytoclastic crisis).

Fitz-Hugh has considered all the various forms of therapy in the treatment of this condition and emphasized that yellow bone marrow concentrate for oral administration is of real value.

The Relation of Sulfanilamide to Granulocytopenia—Since sulfanilamide and its derivatives and allied substances are now commonly used in the treatment of various types of bacterial infection, it becomes increasingly important to consider the etiologic relation of these drugs to the syndrome of granulocytopenia. In 1937 there were 8 and in 1938 there were 9 published articles bearing on this subject.

Schwartz, Garvin and Koletsky²⁸⁷ have reported a case of granulocytopenia which developed after the administration of 48.6 Gm of sulfanilamide over a period of nineteen days. The leukocyte count fell to 800 per cubic millimeter, and no granulocytes were present. The lowest recorded level of the erythrocytes was 3,410,000 per cubic millimeter. Pentnucleotide (10 cc twice daily), liver (5 cc twice daily) administered intramuscularly and a transfusion of 500 cc of whole blood and typhoid vaccine intravenously were given without effect. The patient had a primary syphilitic lesion (probably a reinfection) and had received antisyphilitic therapy. The last dose of neoarsphenamine had been given three years previously, mepharsen was last given fifty-six days before the development of leukopenia, bismuth and mercury had been administered intermittently for more than five years without signs of intolerance. Necropsy showed a maturation arrest of the myeloid series. There was marked phagocytosis of iron in the liver, spleen and bone marrow, which was interpreted as evidence that the anemia was hemolytic.

²⁸⁷ Schwartz, W. F., Garvin, C. F., and Koletsky, S. Fatal Granulocytopenia from Sulfanilamide, *J. A. M. A.* **110** 368 (Jan. 29) 1938.

The case of a man aged 22 who was treated with sulfanilamide for acute gonorrhea was reported by Berg and Holtzman²⁸⁸ The drug was administered in 10 grain (0.65 Gm) doses every four hours After five days the use of this medication was discontinued on account of slight fever, cramps, gaseous eructations and nausea After an interval of four days, it was resumed, with the dose of 5 grains (0.32 Gm) three times daily Seven days later there was a recurrence of the same toxic symptoms, and the use of the medication was again discontinued It was resumed once more, with a dose of 10 grains thrice daily, despite evidences of toxicity After eleven days the patient experienced chill and fever (102 F), and nausea, vomiting and prostration developed The lowest leukocyte count recorded was 1,600 per cubic millimeter (all lymphocytes), the erythrocyte count fell to 2,600,000 per cubic millimeter and the hemoglobin value to 60 per cent We wish to emphasize that this case illustrates the need for the warning which is now well recognized, viz, that if the serious toxic manifestations of the drug, such as nausea, vomiting and fever, occur, they are likely to reappear if use of the drug is resumed after an interval

Long, Bliss and Feinstein²⁸⁹ reported on a patient with gonorrheal urethritis and arthritis who manifested the typical picture of agranulocytic angina toward the end of the third week of treatment with sulfanilamide Procedures designed to rid him of the sulfanilamide were immediately instituted, and recovery followed within ten days These observers recorded the frequency of granulocytopenia as 0.3 per cent in their group of 307 adults and 101 children receiving sulfanilamide therapy

Jones and Miller²⁹⁰ reported the case of a man aged 26 who was given 2.4 Gm of sulfanilamide daily for ten days for acute gonorrhea At the end of this time he had headache, backache and fever (104.4 F), the leukocyte count was between 9,000 and 10,000 per cubic millimeter, and there was moderate injection of the pharynx The use of the drug was discontinued, and the symptoms subsided with the fever, sulfanilamide therapy was resumed, with doses of 0.9 Gm daily, being increased by that amount each day until a daily dose of 3.6 Gm was reached At this time the temperature again rose, and he had the feeling that "he was coming down with a cold" The leukocyte count remained normal Therapy was again stopped, and the symptoms disappeared After an

288 Berg, S, and Holtzman, M Fatal Granulocytopenia Following Sulfanilamide Therapy, *J A M A* **110** 370 (Jan 29) 1938

289 Long, P H, Bliss, E, and Feinstein, W H Mode of Action, Clinical Use and Toxic Manifestations of Sulfanilamide, *J A M A* **112** 115 (Jan 14) 1939 Long, P H, and Bliss, E A Toxic Manifestations of Sulphanilamide, *Ann Surg* **108** 808, 1938

290 Jones, H W, and Miller, C P Neutropenia Following Sulfanilamide Report of a Case, *J Lab & Clin Med* **24** 121, 1938

interval of four days, 2.7 Gm of the drug was administered on one day only. The next morning the leukocyte count was 4,100 per cubic millimeter, with 25 per cent granulocytes. The patient complained of headache, chilliness and general malaise. On the following day the leukocyte count was 2,300, with 5 per cent neutrophils. Yellow bone marrow concentrate, 80 drops daily, was given, after which the leukocyte count rose rapidly. Four days later he was symptomless. It is interesting to note that the sulfanilamide content of the blood was 5.6 and 2.8 mg per hundred cubic centimeters during the second and third periods of intoxication, indicating that an overdosage, in the ordinary meaning of the term, had not been given. The authors concluded that the patient had acquired an increased susceptibility to the drug. The course of events in this case, we believe, illustrates clearly that a febrile reaction which develops during the course of sulfanilamide therapy is a significant warning which cannot be disregarded.

Johnston²⁹¹ reported on 2 patients with granulocytopenia following the use of sulfanilamide whom he had observed and 10 previously reported on in the literature. These were studied in an attempt to discover common features which might help in the prevention, recognition and treatment of this condition. The first case observed by him was that of a woman of 23 years with severe puerperal infection due to *Streptococcus haemolyticus* who was given 61.3 Gm of neoprontosil and sulfanilamide orally and intramuscularly over a period of twenty days. On the eighteenth day of treatment the leukocyte count was found to be 1,520 per cubic millimeter, and no polymorphonuclear neutrophilic cells were present in the blood film. "Marked secondary anemia" was also present. Recovery followed discontinuance of the use of sulfanilamide and prontosil, and the administration of pentnucleotide and a blood transfusion. It is important to record that during her illness, the patient received 10 tablets of allonal (allylisopropylbarbituric acid with aminopyrine), each of which contained 0.03 Gm of aminopyrine, over a period of twenty-one days. The second case was that of a woman aged 33 years with moderately severe puerperal infection due to *Str. haemolyticus* who had been treated with prontosil orally and intramuscularly for three days prior to admission to the hospital. She received a total of 68.45 Gm of sulfanilamide and neoprontosil over a period of twenty-two days. The leukocyte count fell to 3,500 per cubic millimeter, with 41 per cent of the cells of the polymorphonuclear neutrophil series. There was also anemia, as indicated by a hemoglobin value of 56 per cent and a red blood cell count of 2,600,000 per cubic millimeter. She recovered after discontinuance of treatment with sulfanilamide, the administration of pentnucleotide and a blood transfusion. It is noteworthy to record that this patient during her illness

291 Johnston, F. D. Granulocytopenia Following Administration of Sulfanilamide Compounds, *Lancet* 2: 1044, 1938.

also received 5 tablets of allonal over a period of eight days. The observers were cognizant of the possible etiologic relation of allonal to the agranulocytosis in the 2 cases but stated that in these cases it was "not very clear."

Johnston recorded 10 additional cases of granulocytopenia which had been reported up to the time his article was written and tabulated the main details of each. Five more cases which have been less fully reported were also mentioned. He concluded that granulocytopenia with a high mortality rate may occur in certain susceptible persons after or during treatment with the sulfanilamide-prontosil group of drugs. It is not thought necessary to make routine leukocyte counts for all patients receiving these drugs, but frequent examinations of the blood should be made when there is pyrexia or an increase in pyrexia which is already present. It is his conclusion that the duration of treatment is probably a more important factor in relation to the disease than the total dosage of the drug.

McGuire and McGuire²⁹² reported the case of a woman aged 35 with rheumatoid arthritis who received 15 grains (0.97 Gm) of sulfanilamide orally each day for thirty days and then received 5 cc of prontosil (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate) intramuscularly every six hours for three days. Ulceration of the throat and cervical adenopathy developed, and the leukocyte count was found to be 450 per cubic millimeter, with no granulocytes. As the patient denied taking any other drugs which were known to cause granulocytopenia, it was concluded that sulfanilamide may have been the exciting factor in this case. In an effort to prove this causal relation two months after recovery the patient was given 7.5 grains (0.49 Gm) of sulfanilamide daily, and the blood was examined each day at the same time. After five days the total leukocyte count, which had been 13,050 per cubic millimeter, with 82 per cent granulocytes, had decreased to 9,250 per cubic millimeter, with 35 per cent granulocytes. The test was discontinued, although it was not recorded that the patient complained of symptoms. On the day after the use of the drug was stopped, the leukocyte count was 11,450 per cubic millimeter, with 62 per cent granulocytes. It was concluded that these observations were strong evidence that sulfanilamide was of importance in the production of the leukopenia. We believe that such studies as these are highly important and offer the only conclusive evidence that the drug can cause neutropenia, although significant supplementary data may be obtained by clinical studies. It is regrettable but understandable that more frequent leukocyte counts were not made, and the experiment continued until all question of the etiologic relation had been dispelled.

²⁹² McGuire, P. R., and McGuire, J. P. Agranulocytosis Following Use of Sulfanilamide. Report of a Case, *Illinois M J* **73** 425, 1938.

The case of an 11 year old girl with multiple articular involvement associated with fever, anorexia, emaciation and progressive anemia was reported by Alpert and Forbes²⁹³ After the first few days of sulfanilamide therapy there was leukocytosis (27,200 leukocytes, with 94 per cent granulocytes), which they were inclined to attribute to the medication That this is not necessarily the case is indicated by a subsequent greater leukocytosis at a period when the drug had not been given for some time A total dose of 12.2 Gm was administered over a period of one week, and then the treatment was discontinued for a similar interval At the end of that time, after 0.6 Gm had been taken, the leukocyte count was found to be 3,200 per cubic millimeter, with a total disappearance of granulocytes from the circulating blood The patient had a febrile reaction and vomited, oral lesions were present The sulfanilamide treatment was discontinued Convalescent streptococcus serum, three blood transfusions and four intramuscular injections of liver extract were given, and prompt improvement resulted, with subsequent complete recovery from the blood dyscrasia No reference was made concerning the administration of other drugs of etiologic importance, such as aminopyrine, which must be considered as a possibility when the patient is suffering from an acute rheumatic condition

Allen and Short²⁹⁴ reported the development of agranulocytosis in an 18 year old girl during the course of treatment with sulfanilamide for a mild infection, presumably due to the gonococcus There was spontaneous recovery without recourse to any of the recommended forms of therapy for neutropenia In the authors' opinion, no other drugs of etiologic significance were administered, so that sulfanilamide could be considered, at least presumptively, as the cause of the granulocytosis A total dose of 15.9 Gm of the drug was given over a period of nine days without untoward effects After its use was discontinued for eight days, it was resumed on account of the persistence of the vaginal discharge Four hours after she received a dose of 1.0 Gm, fever developed, and after a second dose, the treatment was discontinued Two days later it was resumed again, with a dosage of 2.4 Gm daily for two days At the end of this time the temperature reached 103 F, but there was no evidence of oral or pharyngeal sepsis The leukocyte count was 2,900 per cubic millimeter, with 64 per cent polymorphonuclear neutrophils The use of the drug was then permanently discontinued The white blood cell count continued to decrease, and finally all polymorphonuclear neutrophils disappeared The patient gradually improved and was discharged from the hospital twenty-four days after discontinuing the use of sulfanilamide The

293 Alpert, G. R., and Forbes, R. P. Granulocytopenia and Hyperleucocytosis Following Sulfanilamide Therapy, *J. Pediat.* **12** 605, 1938

294 Allen, J. G., and Short, C. L. Granulocytopenia Associated with Sulfanilamide Therapy, *New England J. Med.* **219** 6, 1938

authors emphasized two points especially with reference to this case. In the first place, there was absolute monocytosis, which they believe is a good prognostic sign, second, the earliest objective sign of granulocytosis was the increase in body temperature. In their opinion, an idiosyncrasy rather than a cumulative toxicity is probably the mechanism in the production of granulocytopenia in these cases.

After a careful consideration of the literature, we believe that the following conclusions regarding the etiologic relation of sulfanilamide to granulocytopenia are warranted:

1. Considering the widespread use of sulfanilamide, there is an extremely small number of patients in whom the syndrome of granulocytopenia develops.

2. Sulfanilamide is usually given to patients with sepsis, which in itself may admittedly cause marked leukopenia.

3. To say that sulfanilamide causes granulocytopenia should mean that the significant alteration in the blood is limited exclusively to a decrease in the number of granulocytes.

4. In some cases in which granulocytopenia following sulfanilamide therapy has been reported, other drugs that are known to produce the syndrome have been administered at the same time. In some cases this information has been included in the report. In others, in which no mention has been made concerning the use of other drugs, it is conceivable that aminopyrine alone or in combination with other drugs may have been given.

5. No one has reported conclusive evidence that sulfanilamide will cause neutropenia when given to any one who has recovered from the syndrome of granulocytopenia.

6. In some instances, granulocytopenia has developed suddenly with the resumption of therapy after an interim of several days. This suggests that the initial dosage may have sensitized the patient and that the subsequent granulocytopenia might be considered properly as an allergic manifestation.

7. An increase in the height of the temperature when fever is already present or the development of fever in a patient who is receiving sulfanilamide should at once suggest the necessity for a careful examination of the blood to determine whether there is an alteration in the absolute number of polymorphonuclear leukocytes.

8. While pentnucleotide, blood transfusions, yellow bone marrow and liver extract may be of value in the treatment of patients who have granulocytopenia following sulfanilamide therapy, it is probable that the most important therapeutic procedure is the early and immediate discontinuance of the use of sulfanilamide.

Other Etiologic Factors—Reznikoff²⁹⁵ considers that there are four factors of importance in the causation of granulocytopenia. These are (1) fatigue, (2) drugs, (3) menstruation and (4) infection. He found that in 11 of 13 cases in which information on this point was obtained, there was a history of fatigue antedating the onset of the granulocytopenia. We desire to emphasize that it is difficult to evaluate the etiologic significance of fatigue, because it may lead to the use of the very drugs which are in themselves known to cause granulocytopenia. Almost every patient in his series had taken aminopyrine, dinitrophenol, arsphenamine or allonal or had received roentgen treatment, which makes difficult the evaluation of fatigue as an etiologic possibility. If it is granted that fatigue may play a role in the causation of the disease other than that of leading to the use of drugs which might produce it, there is no explanation or theory offered as to how it might act. Although he agreed that drugs, especially aminopyrine, are important in causing granulocytopenia, he cited the figures of Jackson, who stated that in 44 per cent of his cases no drugs had ever been used, a statement which, in our opinion, is difficult to prove. Furthermore, the question is raised as to why a drug like aminopyrine may be taken for a considerable period of time without apparent ill effects and then the patient suddenly manifests the disease. He does not consider this in keeping with the present conception of allergy and has stated that if it is a sudden manifestation of an Arthus phenomenon, it must be admitted that the precipitating factor is unknown. This observer considers that in most cases infection is the result rather than the cause of the disease, but he still believes that it must be considered as one of the etiologic agents. Reznikoff believes that menstruation is undoubtedly an important etiologic factor in the disease and has stated that "many cyclical cases have been described in which this was the only etiologic condition and in which no drugs were known to have been used." Although it cannot be denied that menstruation may bear a relationship to the disease, the evidence at best is only presumptive. Here again, in appraising this matter, we believe that the situation is complicated because many women take aminopyrine alone or in association with other drugs for dysmenorrhea.

Reznikoff is in accord with the belief that monocytosis is a favorable prognostic sign in granulocytopenia. Of his 13 patients, 9 recovered, and all had sustained relative and in most instances absolute monocytosis, which in many cases preceded the return of the neutrophil count to normal, the rise in the leukocyte count and the drop in temperature or symptomatic improvement.

²⁹⁵ Reznikoff, P. The Etiologic Importance of Fatigue and the Prognostic Significance of Monocytosis in Neutropenia (Agranulocytosis), *Am J M Sc* **195** 627, 1938.

Two cases of granulocytopenia are reported by Jackson²⁹⁶ in which the etiologic agent appears to have been causalin, a drug made up of approximately equal parts of aminopyrine and hydroxyquinoline, and widely advertised for the treatment of "rheumatism." One patient, a woman aged 67, had been taking 3 tablets of causalin daily for a month. One week before admission to the hospital she had a severe sore throat and fever. The palate and fauces showed marked inflammatory change, the white blood cell count was 1,200 per cubic millimeter, with 4 per cent polymorphonuclear neutrophils. The red blood cell count was 3,300,000 per cubic millimeter and the hemoglobin value 59 per cent. Pentnucleotide, in doses of 40 cc daily, failed to produce improvement, and the patient died sixty hours after entry. A second patient, a woman, had taken 200 tablets of causalin for the relief of arthritis in the three weeks prior to admission to the hospital. Eleven days after the initial dose of the drug was taken, fever and ulcerative lesions of the mouth developed. On entrance the leukocyte count was 1,600 per cubic millimeter, the only granulocytes present were basophils (2 per cent). The red blood cell count was 3,830,000 per cubic millimeter and the hemoglobin value 63 per cent. Recovery followed pentnucleotide therapy. The inherent dangers in the use of causalin, containing as it does both aminopyrine and a quinoline derivative, have been emphasized, and Jackson believes that there is no excuse for its therapeutic use.

Jackson²⁹⁷ reported the case of a woman aged 37 in whom neutropenia developed, as evidenced by a leukocyte count of 1,500 per cubic millimeter, with 20 per cent granular leukocytes. This case is of interest for several reasons. First, the patient had consumed more than 10 gallons (38 liters) of elixir of phenobarbital in the five years prior to the onset of the granulocytopenia and, in addition, had taken an unknown quantity of phenobarbital tablets. Although the blood condition followed the excessive use of a hypnotic drug, there is no evidence that this drug was of etiologic significance in producing the condition. We are of the opinion that there is no convincing proof in the literature that hypnotic drugs alone, especially the barbiturates, will cause granulocytopenia, although many cases have been reported following the use of these drugs when combined with aminopyrine. In such cases it is generally accepted that the aminopyrine rather than the hypnotic drugs is responsible for the granulocytopenia. Furthermore, the possibility must always be considered that a patient who is so unstable as to take such large doses of phenobarbital frequently resorts to hypnotic drugs which may be combined with aminopyrine. Such combinations are readily purchasable in many states in this country without a prescription.

296 Jackson, H, Jr. Agranulocytosis Following Ingestion of Causalin, *J A M A* **111** 523 (Aug 6) 1938

297 Jackson, W C. Case of Neutropenia Following Excessive Use of Phenobarbital, *M Rec* **148** 148, 1938

Second, the case is of interest because there was associated anemia, as indicated by a minimum red blood cell count of 1,850,000 per cubic millimeter and a hemoglobin value of 32 per cent. The author emphasized, very properly, that it is unusual to observe such severe anemia in granulocytopenia and ascribed it to some complicating factor rather than a part of the acute disease. Recovery followed the use of blood transfusions, pentnucleotide and liver extract and the prohibition of hypnotic drugs.

In a man aged 46 years, reported on by Mays,²⁹⁸ leukopenia, with chills and fever and jaundice developed after the administration of twenty-nine injections of arsphenamine, fourteen of neoarsphenamine and fifty-one of bismuth subsalicylate during a period of twenty months. Recovery followed five injections of pentnucleotide, infusions of dextrose and a high carbohydrate diet. The red blood cell count and the hemoglobin value remained within normal limits. In our opinion it is not possible to state definitely that the leukopenia was due to the anti-syphilitic therapy, furthermore, the blood findings are somewhat puzzling and not entirely characteristic of granulocytopenia. On one occasion the leukocyte count was reported as 3,100 per cubic millimeter, "with apparently all very immature cells," on another occasion the leukocyte count was 2,800 per cubic millimeter, with 2 per cent polymorphonuclear leukocytes, 4 per cent metamyelocytes and 28 per cent myelocytes.

Chapman²⁹⁹ reported a fatal case of granulocytopenia, that of a woman aged 43 years, with fever, ulcerative lesions in the throat and a leukocyte count of 650 per cubic millimeter, with only 2 per cent polymorphonuclear cells. The red blood cell count was 3,780,000 per cubic millimeter and the hemoglobin value 70 per cent. The patient died, despite the use of pentnucleotide, parenteral treatment with liver extract and repeated small transfusions of whole blood. The cause of the condition was not discussed, the statement concerning drug therapy was that at the onset of the illness the patient took acetylsalicylic acid, a cathartic and a patent medicine called "H-C" powder, the chemical composition of which was not given.

Shaw³⁰⁰ reported the case of a 64 year old woman with pyrexia, ulcerations of the mucous membranes of the posterior pharyngeal wall, tonsils and fauces, and a maximum reduction in the white blood cell count of 560 per cubic millimeter, with 17 per cent polymorphonuclear leukocytes. There was no statement which indicated positively that the

298 Mays, A. T. Agranulocytosis Following Administration of Arsphenamines and Bismuth. Report of a Case, *New York State J. Med.* **38** 1234, 1938.

299 Chapman, W. H., Jr. Agranulocytosis with Report of a Case, *Virginia M. Monthly* **65** 287, 1938.

300 Shaw, C. C. Granulocytopenia. Report of a Case with Autopsy, *New England J. Med.* **218** 343, 1938.

patient did or did not receive certain drugs of etiologic importance, such as aminopyrine. This case was regarded as one of the group in which the condition can "develop in certain instances without any apparent cause." It is unusual, in our opinion that the ulcerations of the throat developed prior to a decrease in the leukocyte count.

Stites and Stites³⁰¹ observed a woman aged 32 who had fever, an injected throat and some enlargement of the anterior cervical lymph glands. The leukocyte count varied from 2,700 per cubic millimeter on admission to the hospital to 1,450 per cubic millimeter the fourth day afterward. Granulocytes were absent on the seventh day, and the count did not rise above 9 per cent for seven consecutive days. Recovery followed the giving of pentnucleotide and of liver extract parenterally and one blood transfusion of 520 cc. Six weeks before entry she had experienced chills and fever and was treated with quinine, atabrine and plasmochin. The authors implied that the atabrine and plasmochin were the cause of the granulocytopenia. Although this must be admitted as a possibility, we wish to emphasize that there was no conclusive proof to substantiate this assumption. The increasing use of the new preparations in the treatment of malaria and their possible relation to granulocytopenia make this report noteworthy.

The case of a man aged 23, with dementia praecox who was found to have a leukocytic count of 400 per cubic millimeter, with 11 per cent granulocytes, 88 per cent lymphocytes and 1 per cent monocytes was reported by Kitching³⁰². The red blood cell count was 4,500,000 per cubic millimeter, a few normoblasts were present and an occasional cell showed punctate basophilia. No ulcerative lesions of the mucous membranes were apparent during life, but at necropsy the colon was the seat of extensive necrotic lesions which appeared to involve only the mucosa. The sternal bone marrow appeared normal to the naked eye. Smears showed absence of polymorphonuclear cells, but myelocytes and lymphocytes were present. The only drug which the patient had received was soluble barbitol ("sodium barbitone"). The case is reported as one of primary granulocytopenia of unknown causation.

The case of a man aged 18 was reported by LaSalle and LaSalle³⁰³. He was in a coma when admitted to the hospital after three days of illness characterized by fever, sore throat and headache. There were 4,300 leukocytes per cubic millimeter, "of which only 2 per cent were granulocytes of the basophilic series." There were marked hypotension and redness of the throat but no other buccopharyngeal lesion. The patient succumbed one and a half hours after first being observed. No

301 Stites, J., and Stites, F. M. Agranulocytosis, Kentucky M. J. **36** 324 1938

302 Kitching, E. H. A Case of Agranulocytosis, Lancet **1** 83, 1938

303 LaSalle, M., and LaSalle, C. Fulminating Case of Agranulocytosis, M. Rec. **148** 9, 1938

statement was made concerning the use of drugs which might have a bearing on the causation.

Of considerable etiologic importance may be the chance observation by Lawrence and Syverton¹⁰¹ of a cat with only 350 white blood cells per cubic millimeter and no neutrophils in the peripheral blood. The supernatant fluid from a ground-up suspension of the liver of this animal was injected into 5 other cats, and the same blood picture developed in 2 of them. This process was continued until thirteen transmissions were accomplished. After a latent period of five days following the injection, in which the animals appeared normal, there were pyrexia, anorexia and listlessness, coincident with these changes there was marked neutropenia. There were no changes in the red blood cell count, and the platelet count remained normal or increased. After one or two days, at the height of the disease, the animals either succumbed or had an increase in the white blood cell count and recovered. The causative agent, in the opinion of these observers, appeared to be some filtrable agent or a virus.

Therapy.—The observation by Giffin and Watkins¹⁰² that after the administration of yellow bone marrow to patients with "secondary anemia" there was an increase in the number of neutrophils and monocytes in the circulating blood led to the therapeutic use of this substance in cases of granulocytopenia. Twenty-four patients were treated, and 2 of those who received adequate therapy died. The authors believe that the therapeutic results obtained with bone marrow have been sufficiently satisfactory to warrant a continuation of its administration to the exclusion, at least temporarily, of other methods of treatment, such as treatment with liver extract, transfusion and pentnucleotide. A daily dose of 200 to 300 grams (13 to 20 cm.) was recommended; after recovery a daily dosage of 50 to 100 grams (3.3 to 6.5 cm.) was given three or four months or longer to prevent relapse. It is their belief that some substance in the bone marrow may have the power of stimulating the production or maturation of the leukocytes. They emphasized, very properly, that spontaneous recoveries, multiple methods of treatment and inaccurate diagnoses make difficult the accurate appraisal of various forms of therapy in this disease.

The studies of Marberg and Wiles¹⁰³ were inspired by the statement of Dr. C. H. Watkins, of the Mayo Clinic, at the meeting of the American Medical Association in 1933 that yellow bone marrow had been beneficial in cases of granulocytopenia. A nonsaponifiable fraction of yellow bone marrow was prepared and administered to 6 normal persons

101. Lawrence, J. S., and Syverton, J. T. Spontaneous Agranulocytosis in the Cat, *Proc. Soc. Exper. Biol. & Med.* **38**:911, 1938.

102. Giffin, H. Z., and Watkins, C. H. The Administration of Yellow Bone Marrow in Agranulocytic Angina, *Minnesota Med.* **21**:62, 1938.

103. Marberg, C. M., and Wiles, H. O. Granulocytopoietic Fraction of Yellow Bone Marrow, *Arch. Int. Med.* **61**:408 (March) 1938.

without effect on the leukocyte counts Seven patients with leukopenia which was not considered to be true granulocytopenia but was associated with such conditions as aplastic anemia and leukemia showed no response to the administration of the concentrate Six patients with agranulocytic angina (malignant neutropenia) were treated with yellow bone marrow per os, and all recovered The authors concluded that yellow bone marrow concentrate has granulocytopoietic activity sufficient to bring about a normal blood picture when used in cases of agranulocytic angina and of some other leukopenias In our opinion this conclusion does not appear to be well grounded for the following reasons 1 Spontaneous improvement, without relation to therapy, may well have explained why the patients recovered 2 Recovery may well have been due to the discontinuance of the use of aminopyrine, which some of the patients were known to have received, 3 Only 1 of the patients received yellow bone marrow concentrate as the sole granulocytopoietic medication, the others were also given liver extract or pentnucleotide therapy in addition In attempting to appraise different forms of therapy for acute agranulocytic angina, it should be kept in mind constantly that many patients will recover if the cause of the condition, which in the past has most frequently been aminopyrine, is removed

Netousek³⁰⁷ reported that in a case of aminopyrine granulocytopenia, transfusion with blood from a patient with myelogenous leukemia was followed by a good therapeutic result after pentnucleotide and a blood transfusion had failed to produce benefit

Massias and Quat³⁰⁸ observed recovery of a patient following the administration of vitamins A, B and C The white blood cell count was 5,400 per cubic millimeter, and polymorphonuclear cells were absent from the circulating blood The condition was attributed to bismuth therapy which had been used as an antisyphilitic measure Two days after the vitamin therapy had been instituted the granulocyte count had increased to 31 per cent and in five days to 74 per cent

HODGKIN'S DISEASE AND LYMPHOSARCOMA

Webster³⁰⁹ noted periodicity in the recurrence or exacerbation of symptoms in a number of neoplastic conditions, including leukemia, lymphadenoma and Hodgkin's disease Periods of increased growth came in cycles of thirty-three weeks, with a lesser peak at half periods (sixteen and one-half weeks) Half periods were most marked in Hodg-

307 Netousek, M Traitement de l'agranulocytose par le sang leucémique, *Sang* **12** 345, 1938

308 Massias, C, and Phan Huy Quat Guérison rapide d'un syndrome agranulocytaire post-bismuthique par la vitaminotherapie A, B, C, *Sang* **12** 363, 1938

309 Webster, J H D Periodicity in Cancer and Other Neoplastic Diseases (Four Hundred and Fifty Cases), *Brit J Surg* **26** 113, 1938

kin's disease and sarcoma. The data have been interpreted to indicate a virus causation of these diseases.

Bonnet, Thieffry and Montefiore³¹⁰ isolated avian tubercle bacilli from Hodgkin's lymph nodes, while Donati³¹¹ and Vasconcellos³¹² found *Rickettsia* in their material.

In 5.5 per cent of 450 cases of Hodgkin's disease and lymphosarcoma, Decker, Leddy and Desjardins³¹³ found leukopenia (less than 5,500 leukocytes per cubic millimeter). From the point of view of roentgen therapy, leukopenia is not a contraindication to treatment, nor does it have prognostic significance. Initial leukocyte counts between 5,500 and 10,000 occurred in 58.5 per cent of the series and counts above 10,000 in 36 per cent. Polymorphonuclear percentages were higher, with lymphopenia in those cases in which there was an elevated leukocyte count. In the leukopenic normal and leukocytosis patients, the losses in percentage of leukocytes four to eight weeks after irradiation were, respectively, 16 and 9.9 per cent, 22.4 and 33.3 per cent and 58.6 and 50.9 per cent. In the last group the reduction was due primarily to a decrease in the polymorphonuclear level rather than a destruction of lymphocytes.

Edward³¹⁴ studied the cytologic basis of Gordon's encephalitogenic reaction. The agent could be demonstrated in mixtures of myelocytes and older cells from patients with myelocytic leukemia but not in suspensions composed chiefly of myeloblasts. Blood from a patient with eosinophilia gave a strongly positive result. Lymphocytes gave a weakly positive result. Turner, Jackson and Parker³¹⁵ demonstrated that the reaction was definitely caused by eosinophils, and this observation was confirmed by McNaught,³¹⁶ who supported the theory that Gordon's agent and Friedmann's agent are identical and are apparently derived from the eosinophils and not anything specific for Hodgkin's disease.

310 Bonnet, H., Thieffry, S., and Montefiore. Présence d'un bacille tuberculeux de type aviaire dans un ganglion de lymphogranulomatose maligne, *Compt rend Soc de biol* **128** 583, 1938.

311 Donati, A. Etiologie de la lympho-granulomatose aigue de Paltauf-Sternberg, *Soc internaz di microbiol, Boll d sez ital* **9** 318, 1937.

312 Vasconcellos, I. Encore a propos de l'étiologie de la granulomatose aigue Paltauf-Sternberg, *Soc internaz di microbiol, Boll d sez ital* **9** 321, 1937.

313 Decker, F. H., Leddy, E. T., and Desjardins, A. U. Leukopenia and Leukocytosis in Lymphoblastoma, *Am J Roentgenol* **39** 747, 1938.

314 Edward, D. G. Observations on the Cellular Basis of the Gordon Test for Lymphadenoma, *Lancet* **1** 936, 1938.

315 Turner, J. C., Jackson, H., Jr., and Parker, F., Jr. The Etiological Relation of the Eosinophil to the Gordon Phenomenon in Hodgkin's Disease, *Am J M Sc* **195** 27, 1938.

316 McNaught, J. B. The Gordon Test for Hodgkin's Disease. A Reaction to Eosinophils, *J A M A* **111** 1280 (Oct 1) 1938.

Sachs and Steffel³¹⁷ regard the Gordon test as of diagnostic value in Hodgkin's disease but noted that one gland may give a positive reaction whereas another gland from the same patient, with incomplete histologic transformations, may show a negative reaction. In a series of 11 cases of Hodgkin's disease studied by Turner, Jackson and Parker,³¹⁵ the Gordon test gave a positive reaction only when eosinophils were present in the glands used in inoculating the rabbits or guinea pigs. The pathogenic agent described by Friedmann and Elkeles in myeloid tissues was shown to be present only in those suspensions of leukocytic cream that contained more than 2,000 eosinophils per cubic millimeter.

Madding³¹⁸ analyzed 6 cases of Hodgkin's disease in which there was involvement of the stomach. All the patients were men, 38 to 62 years of age. The red blood cell counts varied from 3,740,000 to 4,000,000 per cubic millimeter. Achlorhydria was present in 1 and fever in none. Clinically the condition simulated that of ulcer or carcinoma of the stomach.

In 5 of the cases, treatment consisted of partial or total excision of the stomach and in 1 case of excision of an ulcer. Three patients were living six to eight years after the operation, and 1 was living and well after one year.

Kato and Cardozo³¹⁹ studied a 14 year old Negro boy who died of Hodgkin's disease. The red blood cells showed the sickling phenomenon. As the disease progressed, eosinophilia became marked, terminating with 47 per cent eosinophils (26,000 leukocytes). The authors commented on the relation of multinucleated giant cells and megakaryocytes. They favor the concept of myeloid transformation of the lymph nodes, likening the disease in some respects to myelogenous leukemia. Bingold,³²⁰ who considers Hodgkin's disease as an infectious granuloma, described cases in which the tonsils were involved. He suggested that excised tonsils should be studied carefully for incipient Hodgkin's disease, so that wide dissemination can be forestalled by means of radical surgical intervention and energetic roentgen therapy. Falconer and Leonard³²¹ correlated the incidence and extent of pulmonary involvement with the characteristics and duration of lymphosarcoma, leukemia and Hodgkin's disease. Pulmonary involvement in lymphatic leukemia was 30 per cent, in lymphosarcoma 36 per cent and in Hodgkin's disease

317 Sachs, H. W., and Steffel, W. Ueber die Bedeutung des Gordon-Testes für die Diagnose der Lymphogranulomatose, *Klin. Wchnschr.* **17** 1043, 1938.

318 Madding, G. F. Hodgkin's Disease of the Stomach. Report of Six Cases, *Proc. Staff Meet., Mayo Clin.* **13** 618, 1938.

319 Kato, K., and Cardozo, W. W. Hodgkin's Disease with Terminal Eosinophilia Occurring in a Negro Child with Sickleemia, *J. Pediat.* **12** 165, 1938.

320 Bingold, K. Die Tonsillen als Eintrittspforte und Sitz der Erkrankung bei Lymphogranulomatose, *Deutsches Arch. f. klin. Med.* **182** 338, 1938.

321 Falconer, E. H., and Leonard, M. E. Pulmonary Involvement in Lymphosarcoma and Lymphatic Leukemia, *Am. J. M. Sc.* **195** 294, 1938.

31 per cent The duration of life after the onset of pulmonary involvement in these three diseases was two months to eleven years, four months to four and one-half years, and twenty-two to fifty-one months, respectively Involvement of the pulmonary parenchyma, with pleural effusion, indicated a poor prognosis

Wright³²² reviewed the symptoms in 60 cases of Hodgkin's disease in which there were intrathoracic lesions The diagnosis is made by roentgenographic study The lesions included enlargement of the mediastinal glands (17 patients), involvement of the pulmonary parenchyma (21 patients) and a combination of these Pleural effusion was present in 17 cases The average duration of life of 45 patients who died was forty months (seven weeks to twenty-six years) The average length of life of 23 patients who lived longer than this was sixty months, and that of 21 patients who lived less than forty months was twenty months The average period of survival after the onset of intrathoracic complications was twenty-three months One patient was apparently cured by surgical removal of enlarged cervical glands (no recurrence in eleven years) For treatment, high voltage roentgen therapy, blood transfusions, mercurial diuretics and improved hygiene and diet have some value Kasabach and McAlpin³²³ found mediastinal involvement in 77 of 251 patients with Hodgkin's disease Nineteen showed mediastinal involvement roentgenographically without associated peripheral lymphadenopathy The latter feature became evident on an average of eighteen months later The average period of survival of the group receiving adequate irradiation was five years and four months With inadequate treatment the period of survival was three and one-fourth years and with no treatment three and one-twelfth years A bad prognosis was indicated by generalized distribution of the lesions, osseous invasion, pulmonary and pleural complications and hepatomegaly In the treatment, maintenance of the patient's weight and general well-being are important Blasi³²⁴ also commented on the intrathoracic localization of Hodgkin's disease Varadi's³²⁵ patient had lymphogranulomatous infiltration of the sternum The diagnosis was made by sternal puncture In Font's³²⁶ patient the lesions of Hodgkin's disease appeared

322 Wright, C B Hodgkin's Disease Sixty Cases in Which There Were Intrathoracic Lesions, *J A M A* **111** 1286 (Oct 1) 1938

323 Kasabach, H H, and McAlpin, K R Mediastinal Hodgkin's Disease, *New York State J Med* **38** 171, 1938

324 Blasi, R Localizzazioni endotoraciche della linfogranulomatose, *Quaderni radiol* **2** 123, 1937

325 Varadi, S L'infiltration lympho-granulomateuse du sternum Sur un case de maladie de Hodgkin, *Sang* **12** 106, 1938

326 Font's Abreau, E Un caso de Hodgkin de punto de partida periostico, *Cir ortop y traumatol*, Habana **5** 277, 1937

after injury of the periosteum of the sternum Pessin and Pohle³²⁷ noted an osteomyelitic process of the manubrium and a cutaneous ulcer as the first manifestation of Hodgkin's disease in a 15 year old girl

The character of the fever in Hodgkin's disease was discussed by Michon and Loth³²⁸ and Michon³²⁹ In the case reported by Delmas-Marsalet, Bergouignan and Verger³³⁰ the symptoms were caused by compression of the spinal cord by an intraspinal malignant lymphogranuloma The lesion was not helped by roentgen therapy In Stewart's³³¹ case there was marked involvement of the spinal cord Froment, Croizat and Masson³³² described radiculomedullary compression from a Hodgkin's growth Symptoms due to marked involvement of glandular groups stimulated several case reports cervical, Efskind,³³³ axillary, Merklen, Gounelle and Warter,³³⁴ rectal, Gallart-Mones and Roca de Vinals³³⁵ Sherman³³⁶ has summarized the gastrointestinal manifestations in Hodgkin's disease Osseous lesions marked the cases reported by Heiskovits,³³⁷ Abrams³³⁸ and Teenstra³³⁹ Jutras³⁴⁰ treated 46 patients (25 males and 21 females) who had pharyngeal lymphosarcoma Sixteen of these patients lived five years after roentgen

327 Pessin, S B, and Pohle, E A Hodgkin's Disease with Ulcerative Involvement of the Skin, *Am J Cancer* **34** 220, 1938

328 Michon, P, and Loth De la fièvre dite ondulante au cours de la maladie de Hodgkin, *Rev med de Nancy* **66** 430, 1938

329 Michon, P Fièvre périodique rythmée au cours de la maladie de Hodgkin, *Paris med* **1** 506, 1938

330 Delmas-Marsalet, Bergouignan and Verger Compression de la moelle par granulomatose intra-rachidienne Echec de la radiothérapie, *Bull et mem Soc med et chir de Bordeaux* (1936), 1937, p 467

331 Stewart, H H Hodgkin's Disease with Spinal Cord Involvement. *Ulster M J* **7** 68, 1938

332 Froment, J, Croizat, P, and Masson, R Des compressions radiculomédullaires dans la granulomatose maligne, *J de med de Lyon* **19** 71, 1938

333 Efskind, L Ein Beitrag zur Pathologie der Halslymphdrüsen Unter besonderer Berücksichtigung der "atypischen" Lymphogranulomatose, der Reticuloendotheliosen und der Reticuloendotheliosarkome, *Acta path et microbiol Scandinav* **15** 16, 1938

334 Merklen, P, Gounelle, H, and Warter, J Maladie de Hodgkin avec ramollissement des ganglions axillaires, *Bull et mem Soc med d hop de Paris* **53** 1243, 1937

335 Gallart-Mones, F, and Roca de Vinals, R Lymphogranulome de Hodgkin rectal de forme tumorale, *Arch d mal de l'app digestif* **28** 67 1938

336 Sherman, E D Gastro-Intestinal Manifestations of Lymphogranulomatosis (Hodgkin's Disease), *Arch Int Med* **61** 60 (Jan) 1938

337 Herskovits, E Kasuistische Beiträge, *Röntgenpraxis* **10** 114, 1938

338 Abrams, H S Osseous System in Hodgkin's Disease, *Ann Surg* **108** 296, 1938

339 Teenstra, C P H Hodgkin's Malignant Granuloma with Marked Skeletal Changes, *Nederl tijdschr v geneesk* **82** 391, 1938

340 Jutras, A Protracted Roentgen Therapy of Pharyngeal Lymphosarcoma, *Am J Roentgenol* **39** 792, 1938

therapy The protracted method of Regaud and Coutard was used, with hourly weak dosage and daily exposure (four to twenty-four sittings in sixty-two days) Finzi³⁴¹ advocated repetition of submaximal doses of roentgen rays in the treatment of lymphadenoma (Hodgkin's disease) The treatments are first given within two weeks, then repeated in six to eight weeks and then repeated in three months Repeated submaximal doses are also given to distant parts "When the disease is localized," he concluded, "the patients are curable, and when it is disseminated, they can be relieved" Craver³⁴² found that "fewer but larger doses" of roentgen rays are preferable to protracted cycles of fractional doses Irradiation of the entire body is recommended as an adjunct to local irradiation Of 121 patients, 17 per cent survived five years or longer In 220 cases certain symptoms were noted clinically, as follows pulmonary lesions, 29 per cent, pleural effusion, 17.0 per cent, ascites, 8.0 per cent, jaundice, 6 per cent, itching, 29.0 per cent, cutaneous lesions, 13.8 per cent, herpes zoster, 4.0 per cent, neurologic lesions, 12.0 per cent, and osseous lesions, 18.0 per cent Sacks³⁴³ presented a case of reticulo-endotheliosis and from an analysis of the literature on the subject suggested that the condition is a clinical and pathologic disease entity It resembles Hodgkin's disease and the aleukemic variety of monocytic leukemia, but morphologic and histologic differences are demonstrable

LEUKEMIA

Leavell³⁴⁴ analyzed the records of 136 cases of leukemia in Boston, New York and Philadelphia For 87 patients with chronic myelogenous leukemia the average duration of life was three and one-fifth years and for 49 patients with chronic lymphatic leukemia three and three-fifths years Patients with chronic myelogenous leukemia who had a low leukocyte count, marked anemia or evidence of bleeding had a shorter course than those without these symptoms Marked anemia in lymphatic leukemia indicated an early fatal outcome

Leukemia, at the extremes of life, has been noted by several authors Varela and Gambirassi³⁴⁵ described a subacute blast stage of leukemia

341 Finzi, N. S. The Roentgen Treatment of Lymphadenoma, *Am J Roentgenol* **39** 261, 1938

342 Craver, L. F. Local and General Irradiation in Hodgkin's Disease *Radiology* **31** 42, 1938

343 Sacks, M. S. Systemic Proliferation of the Reticuloendothelial System (Reticuloendotheliosis) Report of a Case and Comments on the Literature, *Arch Path* **26** 676 (Sept.) 1938

344 Leavell, B. S. Chronic Leukemia A Study of the Incidence and Factors Influencing the Duration of Life, *Am J M Sc* **196** 329, 1938

345 Varela, M. E., and Gambirassi, A. C. Mielosis leucemica subaguda a paramieloblastos con metaplasia mieloidea del sistema linfatico, en un niño de 18 meses, *Arch argent de pediat* **8** 1139, 1937

(myelogenous) in an 18 month old infant Hart ³⁴⁶ reported data on acute leukemia in childhood, and Schmid ³⁴⁷ and De and Tribedi ³⁴⁸ made similar observations Simonson ³⁴⁹ analyzed 16 cases of leukemia in childhood Weil, Isch-Wall, Perles and Aschkenasy ³⁵⁰ described cases of leukemia in old age

Spigel ³⁵¹ analyzed 19 cases of leukemia in children (12, acute lymphatic, 2, chronic lymphatic, 5, acute myelogenous) The ages ranged from 1½ to 14 years, and 60 per cent of the patients were females and 40 per cent males Spigel considers that leukemia is a condition secondary to a frequently hidden specific infection in hereditarily susceptible persons

Rhamy ³⁵² studied the blood and tissues of a newborn infant who showed a blood picture with marked erythroblastosis, similar to that in myelogenous leukemia Death was due to rupture of the enlarged spleen (125 Gm) during delivery

From the point of view of causation, Naponen ³⁵³ noted points of similarity between myelogenous leukemia and panmyelophthisis Similar etiologic factors, including severe septic processes and bone marrow poisons (benzene, roentgen rays and radium), are postulated

Struthers ³⁵⁴ reported the details of 7 cases of acute leukemia in China Of these, 4 were cases of lymphatic and 3 of myelogenous leukemia Although leukemia was considered rare in China, the incidence was 1 per six hundred admissions to the medical wards Evans' ³⁵⁵ summary of the evidence of the neoplastic nature of leukemia was as follows 1 Cases are cited in which a tumor became evident before changes in the blood occurred 2 Blood cells in mitosis are seen more frequently in the organs than in the peripheral blood, 3 Invasion of the

346 Hart, F D Acute Lymphatic Leukaemia in Childhood, *Lancet* **1** 1441, 1938

347 Schmid, E Beitrag zur Klinik und Hamatologie der akuten Leukamien im Kindesalter, *Jahrb f Kinderh* **151** 149, 1938

348 De, N N, and Tribedi, B P Lymphatic Leukemia in Children, *Indian J Pediat* **5** 129, 1938

349 Simonson, L M Acute Leukemia in Childhood Analysis of Sixteen Cases, *Wisconsin M J* **37** 110, 1938

350 Weil, P E, Isch-Wall, P, Perles, S, and Aschkenasy, A La leucemie lymphatique chez les vieillards, *Sang* **12** 659, 1938

351 Spigel, H A Leukemias of Infancy and Early Childhood, *Arch Pediat* **55** 7, 1938

352 Rhamy, B W Leukemia in the New Born, with Death at Birth from Traumatic Rupture of the Spleen, *Am J Clin Path* **8** 567, 1938

353 Naponen, P Ueber die Beziehungen der Panmyelophthise zu der akuten myeloischen Leukamie, *Acta med Scandnav*, 1938, supp 89, p 173

354 Struthers, E B Acute Leukemia A Report of Seven Cases, *Chinese M J* **51** 471, 1937

355 Evans, T S Leukemia Some Evidence that Leukemia May Be Allied to New Growth, *J Connecticut M Soc* **2** 112, 1938

tissues by the leukemic cells occurs 4 The cells are sensitive to roentgen and radium irradiation 5 The tendency to skin and bone metastases is marked

Articles on the relation of industrial poisons, mostly benzene, to the production of leukemia were summarized in the section on "Queries and Minor Notes" in *The Journal of the American Medical Association* ³⁵⁶ While the disease has appeared occasionally in persons exposed to benzene or radioactive substances, no relation to exposure to war gas has been reported A case of leukemia following exposure to benzene was described by Perrin, Kissel and Pierquin ³⁵⁷ A case of benzene poisoning in a patient with malarial splenomegaly (Richon, Véran, Girard and Devin ³⁵⁸) and the case of a workman handling betanaphthol (naphthol) (Rolland ³⁵⁹) were reported Cantoni ³⁶⁰ described a case of acute aleukemic lymphadenosis following paratyphoid Lénski ³⁶¹ reported myelogenous leukemia following splenectomy in a patient with malarial splenomegaly associated with polycythemia Conen's ³⁶² patient first showed lymphatic leukemia after an infection with *Streptococcus viridans*

Mangot, Girard and Bousser ³⁶³ studied the blood of a woman who had been a radiologist's assistant for fifteen years and in whom chronic myelogenous leukemia developed In the third year mild leukocytosis (11 000 to 14,000 leukocytes) was noted In the eighth year the leukocyte count reached 19,000 and in the eleventh year 95,000, by the thirteenth year it had reached 120,000 per cubic millimeter Splenomegaly was present A good result was obtained with roentgen therapy

Mallick, Ali and Singh ³⁶⁴ noted myeloid leukemia in patients with earlier tuberculous infection In the case described, marked benefit

356 Industrial Poisons, War Gas and Leukemia, Queries and Minor Notes, J A M A **110** 1508 (April 30) 1938

357 Perrin, M, Kissel, P, and Pierquin, L Leucose aigue benzolique, Paris med **1** 533, 1938

358 Richon, J, Verain, M, Girard, J, and Devin Anémie splénique avec leucoblastose d'origine benzolique chez un paludeen, Rev med de Nancy **66** 349, 1938

359 Rolland, R Leucémie aigue chez un ouvrier manipulant du naphthol, Union med du Canada **67** 262, 1938

360 Cantoni, O Discussione diagnostica di gravi e oscure emopatie Linfadenosi acuta leucemica postinfettiva, Haematologica **18** 1019, 1937

361 Lenski, M Myeloid Leukemia Following Splenectomy in a Patient with Malarial Splenomegaly Associated with Polyglobulia, Polska gaz lek **17** 339, 1938

362 Conen, M Zur Streptokokkengengese der lymphatischen Leukämie, Arch f Kinderh **112** 150, 1937

363 Mangot, G, Girard, L, and Bousser, J Poussees leucocytaires transitoires suivies de leucocytose durable et de leucémie myélogène chez un radiologiste Contribution a la pathogenie et a la prophylaxie de la leucémie myélogène des radiologistes, Sang **12** 569, 1938

364 Mallick, S M K, Ali, S, and Singh, B Myeloid Leucaemia Treated with Deep X-Ray Therapy, Indian M Gaz **73** 19, 1938 -

followed high voltage roentgen therapy over the bones. The authors believe that roentgen rays affect the hemopoietic tissue directly and that the neoplastic formation is checked.

Rosenheim³⁶⁵ described the case of a 56 year old woman in whom pernicious anemia developed. The blood, achlorhydria and symptoms were characteristic, and the response to liver therapy was adequate. The white blood cell count then increased, and typical chronic myelogenous leukemia developed (leukocytes, 93,500 per cubic millimeter). The patient also had tertiary syphilis, but the author considers that the progress of the disease was independent of this and more of the nature of that typical of the disease denoted by the older term leukanemia.

The familial aspects of leukemia have been emphasized by Gottlieb,³⁶⁶ Boggian³⁶⁷ and Shipton³⁶⁸

Complications were illustrated by the cases described by Askanazy³⁶⁹ (diabetes due to leukemic metastases) and by Rachmilewitz³⁷⁰ (polycythemia).

Teng and Chung³⁷¹ found that Leishman-Donovan bodies are phagocytized *in vitro* by neutrophils beyond the myeloblastic stage in leukemic blood and occasionally by eosinophils. Davidsohn²⁸³ noted low titers of isoagglutinins in chronic leukemia, particularly in those cases in which roentgen therapy had not been given. Most patients with acute leukemia or those with chronic leukemia who have received intensive roentgen therapy show normal or slightly elevated titers.

De Lucia and Russo³⁷² found that in acute leukemia there was a diminution of the total, acid-soluble and lipid phosphorus fractions, with no change in the inorganic phosphorus. In chronic leukemia all the phosphorus fractions were definitely increased, in spite of the anemia.

365 Rosenheim, M. L. Myeloid Leukaemia Following Pernicious Anemia and Complicated with Tertiary Syphilis, *Lancet* **2** 1054, 1938

366 Gottlieb, P. Ueber familiares Vorkommen von Leukämie, *München med Wchnschr* **85** 140, 1938

367 Boggian, B. Considerazioni sopra due casi di leucemia familiare, *Policlinico (sez prat)* **45** 472, 1938

368 Shipton, E. A. Familial Leucosis, *M. J. Australia* **1** 116, 1938

369 Askanazy, M. Metastasen, die eine neue essentielle Krankheit schaffen (Morbus Addison und Mycosis fungoides, Diabetes und Leukämie), *Schweiz med Wchnschr* **68** 806, 1938

370 Rachmilewitz, M. Polycythaemia and Leukaemia, *Harefuah* **14** 16, 1938

371 Teng, C. T., and Chung, H. L. Phagocytosis of Leishman-Donovan Bodies by Leukemic Blood Cells, *Proc Soc Exper Biol & Med* **39** 156, 1938

372 de Lucia, P., and Russo, P. Il quadro del fosforo ematico nelle leucemie, *Boll Soc ital di biol sper* **13** 703, 1938

Poole and his associates³⁷³ described in detail the history of a man with chronic myelogenous leukemia, covering a period of nine years. He was treated at intervals with solution of potassium arsenite U S P, roentgen rays or benzene. The authors commented on the fact that it was easier to maintain the white blood cell count within reasonable limits during the hot summer weather than during the winter, but ultraviolet radiation from artificial sources appeared to do harm rather than good. Chemically, the serum minerals were found to be normal. The values for plasma lipids were increased above normal (lipemia). The plasma phospholipid and free cholesterol components were within the normal range. The neutral fat fraction was high, and the cholesterol esters were strikingly low, suggesting a derangement in fat metabolism. The lipid content of the red blood cells was normal, but the sodium and chloride levels were elevated.

Iwatsuru and Nanjo³⁷⁴ found a phosphatase content of leukemic blood that was higher than normal, in proportion to the increase in the number of leukocytes. In myelogenous leukemia, phosphatase is liberated into the serum on destruction of the leukocytes, especially after roentgen therapy. The phosphatase content of the urine increases after roentgen therapy.

In lymphatic leukemia Turner, McAlpin and DeLamater³⁷⁵ reported an increase in the iodine content of the blood, in contrast to the decrease in myelogenous leukemia. Meyer-Bornsen³⁷⁶ noted that there was not a considerable difference in the sulfur content of the leukocytes in the various types of leukemia. Studies of the bone marrow in leukemia were reported by Tuohy³⁷⁷.

Meyer³⁷⁸ found achlorhydria in 13 per cent of the patients with chronic myelogenous leukemia, in 53 per cent of those with chronic lymphatic leukemia and in 33 per cent of those with aleukemic leukemia. In acute leukemia 2 of 5 had achlorhydria. The average ages of the patients with the different types of leukemia were 44, 60 and 51 and one-half

373 Poole, M. W., Erickson, B. N., Williams, H. H., Burkholder, H. J., and Leucutia, T. Ten Years of Treatment and Progress in a Case of Chronic Myeloid Leukemia. The Lipid Distribution in Leukocytes and Erythrocytes, *J. Michigan M. Soc.* **37** 993, 1938.

374 Iwatsuru, R., and Nanjo, K. Ueber den Gehalt des Blutes an Phosphatase bei der myeloischen Leukämie, *Jap. J. M. Sc., VIII, Int. Med., Pediat. & Psychiat.* **4** 334, 1938.

375 Turner, K. B., McAlpin, K. R., and DeLamater, A. Blood Iodine in Leukemia, *Proc. Soc. Exper. Biol. & Med.* **39** 55, 1938.

376 Meyer-Bornsen, A. Ricerche sul solfo organico del sangue. Il solfo totale dei leucociti nelle leucemie, *Biochim. e terap. sper.* **24** 479, 1937.

377 Tuohy, E. L. Bone Marrow Studies, *Journal-Lancet* **58** 74, 1938.

378 Meyer, O. O. Achlorhydria in Leucemia, *J. Lab. & Clin. Med.* **24** 135, 1938.

years, respectively Isaacs³⁷⁹ correlated histologic changes in the lymph nodes in various types of lymphopathy with the clinical features corresponding to them

The neurologic features of leukemia were emphasized in a case described by Nordenson³⁸⁰ A man aged 66 years had diabetes and acute aleukemic myelogenous leukemia Paralysis of the legs developed, followed in two days by paralysis of the hands The terminal picture was marked by severe anemia, leukocytosis (83,000 cells), a predominance of myeloblasts in the blood and bone marrow, fever, stomatitis and hemorrhagic softening of the central ganglions and the anterior horns of the spinal cord Gandellini³⁸¹ described a case of acute leukopenic leukemia in which neurologic symptoms were prominent Touw, Nieuwenhuis and Nauta³⁸² described 2 cases of leukemia characterized by tumor formation They favor the neoplastic causation of the disease

Gibson³⁸³ studied the retinal changes in 22 cases of leukemia The most characteristic features were venous changes, with hemorrhages and exudates The degree of retinal hemorrhages had a prognostic import There was close correlation between the amount of retinal hemorrhage and the degree of anemia Gibson feels that therapy should be directed primarily against the anemia rather than the leukocytosis

In Aylesworth's³⁸⁴ case of lymphatic leukemia, unusual ocular symptoms were noted Cases of chloroma were studied by Frost,³⁸⁵ Barsoum,³⁸⁶ Horsfall³⁸⁷ and Dustin and Thomas³⁸⁸ Cookson and MacRae³⁸⁹ reported a case marked by a lymphoid tumor of the lacrimal

379 Isaacs, R Correlation of Clinical and Laboratory Data in Diseases of Lymph Nodes J Michigan M Soc **37** 1072, 1938

380 Nordenson, N G Les complications nerveuses des leucemies aigues, Sang **12** 605, 1938

381 Gandellini, A Contributo allo studio delle sindromi neuroleucemiche Sudi un caso di leucemia linfatica acuta leucopenica ad insorgenza neurologica, Gazz d osp **59** 650, 1938

382 Touw, J F, Nieuwenhuis, G, and Nauta, J H Two Cases of Leukemia with Tumour-Formation, Acta med Scandinav **97** 376, 1938

383 Gibson, G G Clinical Significance of the Retinal Changes in Leukemia, Arch Ophth **20** 364 (Sept) 1938

384 Aylesworth, F A Unusual Affection of the Eye in Leukaemia, Canad M A J **38** 477, 1938

385 Frost, A D Report of Case with Hematologic Study, Tr Am Acad Ophth **42** 123, 1937

386 Barsoum, H Case of Chloroma, Brit M J **1** 282, 1938

387 Horsfall, R E Chloroma Case History and Postmortem Findings, Brit M J **1** 280, 1938

388 Dustin, P, Jr, and Thomas, J A propos d'un cas de chlorome Etude anatomo-pathologique et biochimique, Sang **12** 1, 1938

389 Cookson, H A, and MacRae, A Lymphoid Tumor of the Lacrymal Gland, Brit J Ophth **22** 385, 1938

gland Alvis³⁹⁰ described leukemic infiltration of the retina and choroid in an infant treated with roentgen rays Dacryocystitis was the first symptom in Stokes' ³⁹¹ case of lymphatic leukemia in a 68 year old man

Thiodet's ³⁹² patient with acute lymphatic leukemia (leukocytes, 193,-600 per cubic millimeter, blasts, 81 per cent) showed predominately abdominal symptoms Subocclusion of the intestine appeared to be the cause, possibly as a result of lymphatic hypertrophy or of primary pressure from enlarged mesenteric nodes or secondarily through interference with nerve function Steinbrinck's ³⁹³ patient showed infiltration of the gastric wall Waitz and Weber ³⁹⁴ reported a case in which phlebitis of the veins of the leg was the first symptom

Brunner and Schnierer ³⁹⁵ and Brunner and Fischer ³⁹⁶ emphasized the part played by the tonsils in myelogenous and lymphatic leukemia

Cutaneous manifestations have been described by Goldsmith ³⁹⁷ and by Riehl ³⁹⁸ in myelogenous leukemia and by Kusunoki and Kuwabara,³⁹⁹ Milbradt ⁴⁰⁰ and Barney ⁴⁰¹ in lymphatic leukemia

Kost and Rachman ⁴⁰² described 2 cases of lymphatic leukemia, in 1 case the prominent features were splenomegaly and mediastinal lymphadenopathy, while enlargement of the mesenteric nodes characterized the other Histologically, however, the features were those of sarcoma

390 Alvis, B Y Leukemic Infiltration of Retina and Choroid in an Infant Treated by X-Ray, *Am J Ophth* **21** 31, 1938

391 Stokes, W H Dacryocystitis in Lymphatic Leukemia, *Arch Ophth* **20** 85 (July) 1938

392 Thiodet, J Leucemie aigue lymphatique avec syndrome de subocclusion intestinale, *Sang* **12** 350, 1938

393 Steinbrinck, W Leukamische Infiltration der Magenwand bei lymphatischer Leukamie, *Folia haemat* **59** 351, 1938

394 Waitz, R, and Weber, A Leucemie lymphoïde subaigue ayant debute par une phlebite du membre inferieur, *Strasbourg med* **98** 231, 1938

395 Brunner, H, and Schnierer, J Die zytologische Untersuchung der Gaumentonsillen und ihre klinische Bedeutung bei Leukamie, *Wien klin Wchnschr* **50** 1772, 1937, Die Untersuchung der Gaumentonsillen bei Leukamien, *Pract oto-rhino-laryng* **1** 36, 1938

396 Brunner, H, and Fischer, J Die Veranderungen der Gaumentonsillern bei Leukamien, *Monatschr f Ohrenh* **72** 137, 1938

397 Goldsmith, W N Chronic Leukaemic Dermatitis, *Proc Roy Soc Med* **31** 79, 1937

398 Riehl, G, Jr Chronische leukamische Myelose mit eigenartigen spezifischen Hauterscheinungen, *Arch f Dermat u Syph* **177** 222, 1938

399 Kusunoki, T, and Kuwabara, S Ueber einen Fall von Scleroderma diffusa, mit Leukamie kompliziert, und durch Parathyreoidektomie gebessert, *Arch f Dermat u Syph* **176** 256, 1937

400 Milbradt, W Klinische Beobachtungen uber seltene Hauterscheinungen bei der lymphatischen Leukamie, *Dermat Wchnschr* **105** 1586, 1937

401 Barney, R E Zosteriform Leukemia Cutis, *Arch Dermat & Syph* **37** 238 (Feb) 1938

402 Kost, E A, and Rachman, V I Sur la clinique des leucemies atypiques, dites etats leucemoides, *Sang* **12** 614, 1938

In these cases there were possible conditions representing forms of lymphosarcoma cell leukemia

Aleukemic Leukemia—Renewed attention has been given to the aleukemic forms of leukemia. Cases have been described by Lindeboom,⁴⁰³ Fujimoto,⁴⁰⁴ Halbron, Lenormand and Jais,⁴⁰⁵ Bazan and Maggi,⁴⁰⁶ Keeler,⁴⁰⁷ and Christen and Grief.⁴⁰⁸ Cabot case 24062⁴⁰⁹ belongs in this group. Miller and Seymour⁴¹⁰ studied 5 cases of leukopenic leukemia and analyzed 18 cases reported in the literature. There was a striking lack of involvement of organs other than the bone marrow. The myeloid tissue showed gross immaturity. Transfusion was the only therapeutic agent of at least temporary value. Weil and Aschkenasy⁴¹¹ described a case of "cryptoleukemia" with an aleukemic blood picture and no splenomegaly or glandular enlargement. The case appeared to be one of severe aplastic anemia, but sternal puncture showed its true nature—aleukemic lymphatic leukemia.

Monocytic Leukemia—Montgomery and Watkins⁴¹² described 4 cases of monocytic leukemia, Schilling type, in which exfoliative dermatitis was a manifestation. A case of monocytic leukemia in a man aged 39 years was described by Beck.⁴¹³ The peculiar configuration of the rosette of vacuoles in the *Hof* of the nucleus on supravital staining, was

403 Lindeboom, G. A. Ueber die sogenannte aleukamische megakaryocytaire Myelose, *Acta med Scandinav* **95** 388, 1938, So-Called Aleukemic Megakaryocystic Myelosis, *Nederl tijdschr v geneesk* **82** 3072, 1938.

404 Fujimoto, M. Ein Fall von acuter myeloischer Leukämie mit geringer Leukozytenzahl im ganzen Verlauf, *Nagasaki Igakkai Zasshi* **16** 1006, 1938.

405 Halbron, P., Lenormand, and Jais. Un nouveau cas de leucose aiguë ayant pris le masque d'une aleucie hemorrhagique. Les difficultés d'interpretation du myelogramme, *Bull et mem Soc med d hop de Paris* **54** 56, 1938.

406 Bazan, F., and Maggi, R. Sobre un caso de linfadenosis aguda aleucemica, *Arch argent de pediat* **9** 385, 1938.

407 Keeler, H. R. Acute Hypocytic Lymphatic Leukemia, *Internat Clin* **3** 271, 1938.

408 Christen, W., and Grief, S. Aleukamische Lymphadenose mit hyperchromer megalozytarer Anämie. Vergleichende Untersuchungen von Sternalmark, Melleolarmark, und peripherem Blut, *Wien Arch f inn Med* **32** 85, 1938.

409 Aleukemic Lymphatic Leukemia, Cabot Case 24062, *New England J Med* **218** 270, 1938.

410 Miller, F. R., and Seymour, W. B. Leukopenic Leukemia of the Myeloblastic Type, *Am J M Sc* **196** 621, 1938.

411 Weil, P. E., and Aschkenasy, A. Un cas de crypto-leucemie lymphatique sans splénomégalie ni adenopathies simulant une anémie grave aplasique, *Sang* **12** 359, 1938.

412 Montgomery, H., and Watkins, C. H. Exfoliative Dermatitis as a Manifestation of Monocytic Leukemia (Schilling), *Proc Staff Meet, Mayo Clin* **13** 294, 1938, *Minnesota Med* **21** 636, 1938.

413 Beck, R. C. Monocytic Leukemia with Analysis of Cell Characteristics by Supravital and Fixed Staining Technics, *Am J Clin Path* **8** 509, 1938.

confirmed as a specific test of the monocytic cells Plum and Thomsen,⁴¹⁴ in describing 3 cases of monocytic leukemia, noted that this disease may be confused at times with infectious mononucleosis or with agranulocytosis They emphasized the points in the differential diagnosis Bouchut, Guichard, Moreau and Mathieu⁴¹⁵ described a case of monocytic leukemia with an acute evolution In cases of monocytic leukemia Wyckoff⁴¹⁶ reported the results of studies of the cells in the blood or bone marrow by means of supravital stains The monocytic cells showed a nucleus with reticular chromatin and one or two nucleoli The peroxidase test gave reactions which varied from heavy to negative Newns and Signy⁴¹⁷ reported on the clinical and histologic aspect of monocytic leukemia in 2 children, 2 and 2½ years old, respectively The course was acute, with death in ten and six and one-half days, respectively Waitz and Hoerner⁴¹⁸ described an aleukemic leukemoid blood picture in a man whose bone marrow contained many large reticulum cells The internal organs and the eyes showed hyperplasia of the "reticuloendothelial" cells Symmers⁴¹⁹ described 4 cases of giant follicular lymphoblastoma Clinically the symptoms resembled those of Hodgkin's disease, certain forms of lymphosarcoma and lymphatic leukemia Histologically there was dimensional hyperplasia of the lymph follicles of the lymph nodes and spleen The author considers the condition to be of "toxic" or "inflammatory" origin and amenable to mild roentgen therapy Transformation to polymorphous cell sarcoma, Hodgkin's disease and the changes of lymphatic leukemia may be sequelae The previously undescribed phase of the evolution of the disease is necrotic folliculitis of the lymph nodes and spleen

Isaacs⁴²⁰ placed the cell called promyelocyte in the monocytic series and described it as typical of the stage after the monocyte blast (metamonoblast)

414 Plum, P, and Thomsen, S Three Cases of Monocytic Leukaemia, *Acta med Scandinau* **96** 578, 1938

415 Bouchut, L, Guichard, A, Moreau, and Mathieu Leucémie a monocytes d'évolution aigue, *Lyon méd* **161** 317, 1938

416 Wyckoff, H A Monocytic Leukemia Some Blood and Bone Marrow Studies, *California & West Med* **48** 348, 1938

417 Newns, G H, and Signy, A G Two Cases of Monocytic Leukaemia, *Proc Roy Soc Med* **31** 364, 1938

418 Waitz, R, and Hoerner, G Syndrome agranulocyttaire avec myeloblastemie et prolifération reticulo-endothéliale medullaire, visceral, oculaire Interêt diagnostique de cette prolifération, *Sang* **12** 801, 1938

419 Symmers, D Giant Follicular Lymphadenopathy With or Without Splenomegaly Its Transformation into Polymorphous Cell Sarcoma of the Lymph Follicles and Its Association with Hodgkin's Disease, Lymphatic Leukemia and an Apparently Unique Disease of the Lymph Nodes and Spleen—a Disease Entity Believed Heretofore Undescribed, *Arch Path* **26** 603 (Sept) 1938

420 Isaacs, R Diagnosis of Leukemia and Response to Therapy *Univ Hosp Bull*, Ann Arbor **4** 129, 1938

Leukemia and Pregnancy—Erf and Fine ⁴²¹ reported the thirty-first case recorded in the literature of a pregnant woman with leukemia. This patient with chronic myelogenous leukemia received intensive roentgen therapy while she was five and one-half to six months pregnant. Six weeks later labor was induced surgically and a normal boy delivered. The mother died seven months later in the stage of myeloblastic leukemia. Although the uterus received at least 200 roentgens, the child did not show any ill effects. Repeated studies of the bone marrow were made on the mother and child.

Forkner ⁴²² discussed the relation of leukemia to pregnancy and the puerperium.

Treatment of Leukemia—Cooke ⁴²³ treated patients with acute leukemia with extracts of fresh red bone marrow. The patients also received blood transfusions and other symptomatic treatment. Two patients had complete remissions for from two to four months, 2 had remissions for shorter periods, 2 showed an increase in the maturation stage of the polymorphonuclear cells, 4 showed arrest of the disease clinically for from three to six months, and 2 showed a decrease in the size of the leukemic lymph nodes and spleen. Other patients, however, showed no effect. The author believes that the course of the disease was influenced definitely in some cases but gave a rather guarded opinion as to the part played by the marrow extract.

For the aleukemic forms of leukemia, Fricke and Watkins ⁴²⁴ recommended radium therapy over the region of the spleen rather than roentgen therapy. Fifteen of 16 patients (leukopenic phases of chronic myeloid and lymphatic leukemia, monocytic leukemia and subleukemic splenic reticuloendotheliosis) showed improvement in the condition of the blood and symptoms. Gosio ⁴²⁵ transfused blood from patients with myelogenous leukemia into patients with lymphatic leukemia and vice versa. When normal blood was used in a transfusion to a patient with lymphatic leukemia, the number of red blood cells increased, when blood from a patient with lymphatic leukemia was given to a patient with lymphatic

421 Erf, L. A., and Fine, A. Serial Blood and Bone Marrow Findings of an Eight Month Premature and Its Roentgen Ray Treated Chronic, Myeloid Leukemic Mother, *Am J M Sc* **195** 8, 1938.

422 Forkner, C. E. The Relationship of Leukemia to Pregnancy and the Puerperium, *Internat Clin* **2** 29, 1938.

423 Cooke, J. V. Experimental Therapy of Acute Leukemia with Extracts of Bone Marrow, *J Pediat* **13** 651, 1938.

424 Fricke, R. E., and Watkins, C. H. The Radium Treatment of Rare Forms of Leukemia, *Proc Staff Meet, Mayo Clin* **13** 193, 1938, *Minnesota Med* **21** 96, 1938.

425 Gosio, R. Le trasfusioni interleucemiche dal punto di vista della regolazione biologica dei tessuti iperleucoplastici, *Polislinico (sez med)* **45** 285, 1938, Ulteriore contributo allo studio della fisiopatologia del leucemico. Ricerche complementari alle trasfusioni interleucemiche, *ibid* **45** 42, 1938.

leukemia, the leukocytosis became more marked. When the blood from a patient with myelogenous leukemia was used, the leukocytosis remained unchanged. The myeloid cells disintegrated, and their products disappeared from the blood stream in from eighteen to twenty hours. The lymph nodes served as the filtering mechanism. A number of other transfusion experiments with leukemic blood have been described. Galán Conesa and Montero⁴²⁶ used polycythemic blood in treating leukemia. Ravina⁴²⁷ used leukemic blood in the treatment of agranulocytosis. A lasting therapeutic result was noted only in their last patient.

Mauro⁴²⁸ noted little therapeutic effect when ascorbic acid was given to patients with Werlhof's disease, myelogenous leukemia or acute or chronic lymphatic leukemia. The amount of ascorbic acid in the urine gave no definite information about the condition in these diseases. Thiele⁴²⁹ found no lasting effect on the leukocyte count when vitamin C was given intravenously, although there was a temporary increase in the number. The medication had no effect on chronic myelogenous leukemia.

Leukemoid Conditions—DuBois⁴³⁰ described the leukemoid condition produced in a man of 53 years by carcinoma of the bladder with metastasis to the lungs and prostate. The leukocyte count was 119,437 per cubic millimeter, with 73.75 per cent mature polymorphonuclear neutrophils. There were no metastases to the bone marrow.

An eosinophilic leukemoid reaction appeared in Recchia's⁴³¹ case of acute colitis. In Leibowitz's⁴³² patient, tuberculous sepsis was accompanied by a myeloblastic blood picture.

Leukemia in Animals—Morton and Mider⁴³³ noted lymphomatosis in 10 of 48 mice painted with methylcholanthrene in solution in commercial benzene. In 2 cases the leukocyte count rose to 90,000 and 139,000.

426 Galán Conesa, E., and Montero, R. Contribucion al estudio de las trasfusiones de globulos. Un caso de leucemia dinfoide temporalmente convertido en policitemico, Bol Soc cubana de pediat **9** 547, 1937.

427 Ravina, A. Agranulocytose. Traitement par la transfusion de sang leucémique, Presse med **45** 1760, 1937.

428 Mauro, E. L'acido ascorbico in alcune emopatie, Minerva med **2** 613, 1938.

429 Thiele, W. Die Wirkung des Vitamin C auf das weisse Blutbild und die chronische myeloische Leukämie, Klin Wchnschr **17** 150, 1938.

430 DuBois, A. H. Leucocytose carcinomateuse pseudo-leucémique, Sang **12** 317, 1938.

431 Recchia, F. Reazione leucemoide ad impronta eosinofila in corso di colite acuta, Policlinico (sez prat) **45** 369, 1938.

432 Leibowitz, S. Tuberculous Sepsis with Myeloblastic Blood Picture, Arch Path **25** 365 (March) 1938.

433 Morton, J. J., and Mider, G. B. The Production of Lymphomatosis in Mice of Known Genetic Constitution, Science **87** 327, 1938.

per cubic millimeter, respectively. No tumors appeared in 50 control mice.

Lewis⁴³⁴ was able to transplant, through twelve generations of mice, three sarcomas induced by the injection of 1, 2, 5, 6-dibenzanthracene. The tumors could not be propagated by means of the injection of blood plasma or with centrifuged tumor extracts.

Lits, Kirschbaum and Strong⁴³⁵ noted regression of a malignant lymphoid tumor in mice, with prolongation of life (fifty and one-half instead of thirty-one and one-half days) after the injection of colchicine. A series of "caryoclastic shocks," with pyknosis and death of the lymphocytes of the tumor, was observed. Normal thymic lymphocytes were also destroyed. Engelbreth-Holm and Frederiksen⁴³⁶ produced leukemia in 36 of 59 mice 4 weeks old by the injection of a cell-free extract of tissues from leukemic mice. The material was prepared by a special anaerobic technic, being reduced with cobalt-cysteine. This experiment seemed to indicate that mouse leukemia, like fowl leukemia, may be transmitted by a chemical rather than a cellular medium. These authors⁴³⁷ concluded that the agent of fowl leukosis is inactivated by oxidation. If the process is interrupted before it is complete, it is possible to reactivate the material almost to its original potency with a cysteine cobalt sulfate reducing system. These data are interpreted to favor a chemical rather than a living (micro-organism) causative agent of fowl leukosis.

Potter, Taylor and MacDowell⁴³⁸ were able to transmit immunity to mouse leukemia from cell-immunized mice to normal mice by implantation of tissue from actively immunized mice. Hall and Knocke⁴³⁹ were able to transmit chloroleukemia in mice by the intravenous injection of a suspension of leukemic cells. While subcutaneous inoculation produced a slowly growing tumor, intravenous injection was followed by generalized leukemia. The greenish color of the lymph nodes was not

434 Lewis, M. R. Transplantable Lymphosarcoma in Mice, *Am J Cancer* **34** 399, 1938.

435 Lits, F. J., Kirschbaum, A., and Strong, L. C. Action of Colchicine on a Transplanted Malignant Lymphoid Neoplasm in Mice of the C3H Strain, *Am J Cancer* **34** 196, 1938; Action of Colchicine on a Malignant Lymphoid Neoplasm in Mice of an Inbred Strain, *Proc Soc Exper Biol & Med* **38** 555, 1938.

436 Engelbreth-Holm, J., and Frederiksen, O. The Transmission of Mouse-Leucaemia to Healthy Animals by Means of Cell-Free Substance, *Acta path et microbiol Scandinav*, 1938, supp 37, p 145.

437 Engelbreth-Holm, J., and Frederiksen, O. The Reactivation of the Fowl-Leukosis Agent After Inactivation by Oxidization, *Acta path et microbiol Scandinav*, 1938, supp 37, p 138.

438 Potter, J. S., Taylor, M. J., and MacDowell, E. C. Transfer of Acquired Resistance to Transplantable Leukemia in Mice, *Proc Soc Exper Biol & Med* **37** 655, 1938.

439 Hall, J. W., and Knocke, F. J. Transmission of Chloroleukemia of Mice, *Am J Path* **14** 217, 1938.

due to eosinophils. After exposures to roentgen rays, the immunity of mice to subcutaneous inoculations was decreased.

Breidis and Furth⁴⁴⁰ were able to preserve mouse leukemic cells at -70°C for as long as four hundred and thirty days and produce lesions on intravenous or subcutaneous inoculations. The types used included lymphoid leukemia (eight to four hundred and forty days), myelocytic leukemia (twenty to four hundred and forty days), chlorioleukemia (one to thirteen days) and monocytic leukemia (two to four hundred and thirty days). Breidis and Furth consider that it is the living leukemic cell which is preserved, and not only a virus. They noted that the cells can be inactivated by roentgen rays while in the frozen state, a feature not characteristic of a virus. Bichel⁴⁴¹ was able to cultivate cells of mouse leukemia in vitro for at least five months by adding actively growing cultures of fibroblasts. A single addition of fibroblasts enabled the cells to grow actively for ten to twelve generations. Division was by mitosis. The cells were easily injured but when injected into mice produced the disease. Yudina⁴⁴² gave weekly injections of a 0.5 per cent solution of 1, 2, 5, 6-dibenzanthracene subcutaneously to 45 chickens for five months. Of these, 1 had leukemia, 3 had aleukemic myelosis, 1 of which also had sarcoma, and 1 had uncomplicated sarcoma. The condition in 1 chicken recalled that of a patient of Ahlstrom's⁴⁴³ who had reticular cell sarcoma and lymphatic leukemia.

Clapham⁴⁴⁴ observed that leukemic fowl showed forty times heavier infestation with tapeworm than normal fowl. Clapham interpreted this to indicate a reduced resistance to tapeworm as a manifestation of the leukemia. Rask-Nielsen⁴⁴⁵ studied the transmission of a neoplasm which consisted of pathologic myeloblasts. The white rats died after about twenty-three days and showed multiple tumors in the abdominal organs. Stasney and Feldman⁴⁴⁶ studied the evolution of leukemic lymphoblastoma in a 3 month old calf. There was general lymphadenopathy, and the histologic details of the tissues resembled those of lymphatic leukemia of man. The leukocyte count was 24,000 per cubic milli-

440 Breidis, C., and Furth, J. The Feasibility of Preserving Neoplastic Cells in the Frozen State, *Science* **88** 531, 1938.

441 Bichel, J. Dauerzuchtung von leukamischen Zellen in vitro, *Ztschr. f. Krebsforsch.* **48** 92, 1938.

442 Yudina, N. D. Leukosis of Chickens Induced by Injections of Carcinogenic Agent 1, 2, 5, 6-diBenzantracene, *Med. zur* **7** 819, 1937.

443 Ahlstrom, C. G. Gleichzeitiges Vorkommen eines Retikelzellsarkoms und einer lymphatischen Leukämie, *Virchows Arch. f. path. Anat.* **301** 49, 1938.

444 Clapham, P. A. The Relation of Helminthiasis to Leukaemia in Domestic Fowls, *J. Helminthol.* **16** 53, 1938.

445 Rask-Nielsen, R. Experimental Studies on a Transplantable Aleukemic Myelomatosis in White Rats, *Acta path. et microbiol. Scandinav.* **15** 285, 1938.

446 Stasney, J., and Feldman, W. H. Leukemic Lymphoblastoma in a Calf. A Hematologic and Histologic Study, *Am. J. Cancer* **34** 240, 1938.

meter, with 68 per cent immature lymphocytes Furth and Furth ⁴⁴⁷ noted monocytic leukemia in 9 of 96 mice which were given 1, 2 benzpyrene intrasplenically The incidence of myelogenous leukemia was greater than that in the controls, although a causal relation was not definite The Rask-Nielsens ⁴⁴⁸ were unable to demonstrate a specific agent by the injection of killed leukotic cells into irradiated and non-irradiated mice Lanza ⁴⁴⁹ produced myelogenous leukemia in rats by the injection of 1, 2 benzpyrene into the bone marrow, Píkovski and Doljanski ⁴⁵⁰ reported similar results

The basal metabolic rate was found by Olson and Dukes ⁴⁵¹ to be slightly increased in transmissible fowl leukosis and fibrosarcoma and greatly increased in lymphosarcoma

Victor and Potter ⁴⁵² found that the serum dextrose value (heart blood) for leukemic mice (ether anesthesia) varied from 38 to 129 mg per hundred cubic centimeters, as compared with 159 to 284 mg in normal and immune mice Neither the administration of dextrose nor that of adrenal cortical extract prolonged the life of leukemic mice These authors ⁴⁵³ also found that the respiratory rate of normal lymphatic tissue and several transmission lines of lymphatic leukemia is depressed by dextrose The amount of depression varied with the transmission line There appeared to be no correlation between the changes in the respiratory quotient produced by dextrose and in the glycolytic rates of cells of lymphatic leukemia tissue

Victor and Potter ⁴⁵⁴ noted that when 0.2 per cent dextrose was added to cells of mouse lymphatic leukemia in leukemic serum, anaerobic glycolysis was about three times greater than when normal serum was used When no dextrose was added, the oxygen consumption was

447 Furth, J, and Furth, O B Monocytic Leukemia and Other Neoplastic Diseases Occurring in Mice Following Intrasplenic Injection of 1, 2-Benzpyrene, *Am J Cancer* **34** 169, 1938

448 Rask-Nielsen, H C, and Rask-Nielsen, R Further Studies on a Transmissible Myeoid Leukosis in White Mice, *Acta path et microbiol Scandinav* **15** 169, 1938

449 Lanza, G Quadri leucemici nei ratti da iniezioni intramidollari di 1, 2 benzopirene Effetti della inoculazione di sangue ed organi di ratti con leucemie da 1, 2 benzopirene in ratti normali, *Pathologica* **30** 185, 1938

450 Píkovski, M, and Doljanski, L Leukaemia Produced by Cancerogenic Substance Preliminary Note, *Haefuah* **14** 21, 1938

451 Olson, C, and Dukes, H H The Basal Metabolic Rate of Chickens Affected with Fowl Paralysis, Transmissible Fowl Leucosis and Certain Spontaneous Neoplasms, *Folia haemat* **60** 57 1938

452 Victor, J, and Potter, J S Low Serum Glucose in Leukemic Mice, *Am J Cancer* **33** 578, 1938

453 Victor, J, and Potter, J S The Respiratory Quotients of Normal and Leukemic Mouse Lymphoid Tissue, *Am J Cancer* **32** 554, 1938

454 Victor, J, and Potter, J S Leukemic Cell Metabolism in Serum of Normal, Immunized and Leukemic Mice, *Am J Cancer* **33** 568, 1938

greater than the carbon dioxide elimination. This is just the reverse of the condition in normal or immune serum. In normal serum, leukemic and normal lymphoid cells have higher respiratory rates than in Ringer's solution, while the anaerobic glycolytic rates are the same in the two mediums. Butler and Warren⁴⁵⁵ noted quick recovery from paralysis and a return of the blood picture to normal in leukemic fowls given injections of 1 or 2 cc of cold pressed wheat germ oil in the breast. Cole,⁴⁵⁶ however, was unsuccessful in this respect when he injected wheat germ oil intraperitoneally.

NIEMANN-PICK DISEASE SCHULLER-CHRISTIAN DISEASE, GAUCHER DISEASE, AND LIPOID HISTIOCYTOSIS

An extensive review of the clinical and physiologic features of the xanthomatous diseases, including Niemann-Pick disease, Gaucher's disease and Hand-Schüller-Christian disease, was given by Thannhauser and Magendantz.⁴⁵⁷ The data are illustrated with material on 22 cases, and a bibliography of one hundred and fifty-nine articles is given. General consideration of the pathologic features of the lipoidoses has also been given by Epstein⁴⁵⁸ and Muller.⁴⁵⁹

Naegeli⁴⁶⁰ analyzed the geographic distribution of various hemopoietic dyscrasias. In addition to the more common diseases, data on some of the more unusual forms were given. A group of over 100 cases of ovalocyte anemia were reported from Danzig, and 11 cases of Hand-Schüller-Christian disease were reported from Debrecen, Hungary.

Sternal puncture material may be of aid in the diagnosis of Gaucher's disease. Scharf-Hansen⁴⁶¹ demonstrated the characteristic cells in the marrow of 2 patients. The marrow itself was hyperplastic, with a relative increase in "macroblasts" and an increase in the relative percentage of erythroblasts as compared with that of the leukopoietic cells. Erf⁴⁶²

455 Butler, W. J., and Warren, D. M. Fowl Leucemia and Vitamin E. A Preliminary Report, *J. Am. Vet. M. A.* **45** 204, 1938.

456 Cole, R. K. Vitamin E and Avian Neurolymphomatosis, *Science* **88** 286, 1938.

457 Thannhauser, S. J., and Magendantz, H. Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of Twenty-Two Cases, *Ann. Int. Med.* **11** 1662, 1938.

458 Epstein, E. Beiträge zur Pathologie der allgemeinen Lipoidosen, *Ergebn. d. allg. Path. u. path. Anat.* **33** 280, 1937.

459 Muller, H. Ueber die sogenannten primären Lipoidosen, *Ztschr. f. Kinderh.* **59** 476, 1938.

460 Naegeli, O. Geographisch-medizinische Erforschung der Anaemien, in *Comptes rendus de la troisième Conference internationale de pathologie géographique*, Helsingfors, Mercator Tryckeri, 1937, p. 81.

461 Scharf-Hansen, H. Sternalpunktion bei Morbus Gaucher, *Folia haemat.* **61** 180, 1938.

462 Erf, L. A. Studies of Gaucher Cells by the Supravital Technique. *Am. J. M. Sc.* **195** 144, 1938.

found Gaucher cells in sternal puncture material from 5 patients, 1 patient had myelocytes and myeloblasts in the blood stream, 1 had no palpable enlargement of the liver or spleen and 1 was severely jaundiced. On supravital staining, the Gaucher fibrils in the cell cytoplasm were often S shaped, with tapered extremities, they were 5 to 10 microns in length and 0.5 to 1.0 microns in width.

Clinical and chemical studies of Gaucher's disease are reported by Zehnder ⁴⁶³ and by Pachman ⁴⁶⁴. Webster ⁴⁶⁵ described a case of Gaucher's disease in a 6 year old girl. The spleen was removed. Six and a half years later the patient appeared well, although there was some increase in pigmentation. The patient reported on by Pack and Silverstone ⁴⁶⁶ also showed improvement after splenectomy.

Freudenberg ⁴⁶⁷ made studies of the blood and tissues of identical twins dying of Niemann-Pick disease. Increased esterase and high phosphatase values were found for the blood serum. The findings did not suggest that the lipid abnormality depended on deficient enzyme action.

Teunissen and den Ouden ⁴⁶⁸ concluded that the phosphatide stored in the spleen in Niemann-Pick disease is sphingomyelin and that the lecithin increase is secondary and smaller. Cases were described by Lignac and Teunissen, ⁴⁶⁹ Loebell ⁴⁷⁰ and Atkinson ⁴⁷¹.

Kato ⁴⁷² studied a 9 month old girl with Niemann-Pick disease. Symptoms were noted at the age of 3 months. Dried splenic substance showed 3.08 per cent lecithin. From the spleen in Niemann-Pick

463 Zehnder, M. Klinischer und chemischer Beitrag zum Studium des Morbus Gaucher, *Deutsche Ztschr f Chir* **250** 422, 1938.

464 Pachman, D. J. Chronic Gaucher's Disease, *Am J Dis Child* **56** 248 (Aug) 1938.

465 Webster, R. Pathological Reports from Children's Hospital, Melbourne V. Gaucher's Disease, *M J Australia* **2** 22, 1938.

466 Pack, G. T., and Silverstone, S. M. Gaucher's Disease. Report of a Case Improved After Splenectomy, *Am J Surg* **41** 77, 1938.

467 Freudenberg, E. Klinische Beobachtungen und Untersuchungen an einem Zwillingsspaar mit Niemann-Pickscher Krankheit (NPK), *Ztschr f Kinderh* **59** 313, 1937.

468 Teunissen, P. H., and den Ouden, A. Contributions to the Study of Phosphatide Lipoidosis (Niemann-Pick's Disease), *Nederl tijdschr v geneesk* **84** 2406, 1938.

469 Lignac, G. O. E., and Teunissen, P. H. Beitrag zur Kenntnis der Lipoidosis phosphatidica, *Beitr z path Anat u z allg Path* **101** 139, 1938.

470 Loebell, H. Niemann-Picksche Erkrankung und Ohr, Hals-, Nasen- u Ohrenarzt (Teil 1) **29** 119, 1938.

471 Atkinson, F. R. B. Niemann-Pick's Disease, *Brit J Child Dis* **34** 245, 1937.

472 Kato, S. A Case of Niemann-Pick's Disease, *Acta pædiat japon* **44** 533, 1938.

disease, Chargaff⁴⁷³ isolated a substance which had marked anticoagulant properties. Chemically the material was a sulfuric acid ester. Wood⁴⁷⁴ described a case of Niemann-Pick disease in an 8 month old white girl. At autopsy there was, in addition to the generalized xanthomatosis, primary carcinoma of the liver (hepatic cell type).

Kennedy⁴⁷⁵ summarized the clinical features of 8 cases of Schuller-Christian disease. The xanthomatous changes were widespread in the organs and tissues, and the skull was involved in all the cases. The blood lipid values did not vary significantly from normal. Rapid healing followed radium or roentgen therapy. Cases of Schuller-Christian disease were described by Aboulker, Bertrand-Guy and Faraggi,⁴⁷⁶ Benedek,⁴⁷⁷ Hallervorden,⁴⁷⁸ Marinescu, Draganescu, Stroesco and Palade,⁴⁷⁹ Vampire, Villaca and Delape,⁴⁸⁰ Miyaji,⁴⁸¹ Shea,⁴⁸² van Bogaert,⁴⁸³ Warburg,⁴⁸⁴ Weissenborn and Wurm,⁴⁸⁵ Wynkoop and Hadley⁴⁸⁶ and Hankey.⁴⁸⁷

473 Chargaff, E. Studies on the Chemistry of Blood Coagulation. VIII. Isolation of a Lipid Inhibitor of Blood Clotting from the Spleen in a Case of Niemann-Pick's Disease, *J Biol Chem* **125** 677, 1938.

474 Wood, H. Generalized Essential Xanthomatosis (Type Niemann-Pick) Associated with Primary Carcinoma of the Liver in an Infant, *Arch Path* **26** 873 (Oct) 1938.

475 Kennedy, R. L. J. Xanthomatosis. Schuller-Christian's Disease, *Proc Staff Meet, Mayo Clin* **12** 776, 1938.

476 Aboulker, H., Bertrand-Guy and Faraggi. Deux cas de maladie de Schuller-Christian, *Bull et mem Soc de radiol med de France* **25** 721, 1937, *Algerie med* **42** 36, 1938.

477 Benedek, L. Hand-Schuller-Christian Syndrome, *Orvos hetil* **82** 211, 1938.

478 Hallervorden, J. Gehirnbefunde bei Christian-Schüllerscher Krankheit und allgemeinen Cholesterinosen, *Ztschr f d ges Neurol u Psychiat* **161** 384, 1938.

479 Marinescu, G., Draganescu, S., Stroesco, G., and Palade, G. Examen anatomo-clinique d'un cas atypique de la maladie de Schuller-Christian, *Ann d'anat path* **14** 673, 1937.

480 Vampire, E., Villaca, C. M., and Delape, J. B. Molestia de Hand-Schuller-Christian, *Rev Assoc paulista de med* **11** 293, 1937.

481 Miyaji, S. Experimentelle Beiträge zur Frage der xanthomatösen Erkrankungen, *Arch f klin Chir* **192** 190, 1938.

482 Shea, J. J. Xanthomatosis (Schuller-Christian's Disease). Report of a Case with Radiosensitive Pathology in Mastoid, *Laryngoscope* **48** 589, 1938.

483 van Bogaert, L. Les aspects neurologiques des cholesterinoses generalisees, *Bull Acad roy de med de Belgique* **3** 206, 1938, *Progrès med*, May 28, 1938, p 785.

484 Warburg, E. Case of Hand-Schuller-Christian's Disease, *Ugesk f læger* **100** 749, 1938.

485 Weissenborn and Wurm, H. Lipoidgranulome des Schädeldachs ohne allgemeine Lipoidgranulomatose (Hand-Schuller-Christiansche Krankheit) bei generalisierter Tuberkulose, *Chirurg* **10** 462, 1938.

BONE MARROW

Weil and Perles⁴⁸⁸ published an illustrated monograph on the findings for different diseases on sternal puncture. Reiter⁴⁸⁹ called attention to the nonhomogeneous distribution of the marrow in the sternum in aplastic anemia, granulocytopenia and myelophthisis, as compared to the uniform changes in leukemia and pernicious anemia. In those cases in which there is irregular distribution of the marrow, sternal puncture may give misleading pictures and result in misinterpretation. Osgood⁴⁹⁰ proposed a nomenclature for blood and bone marrow cells. The differential points in the identification of each type of cell were given in analytic tables. The new names differ from the standard nomenclature (e g, red blood cell is akaryocyte, and polymorphonuclear neutrophil is lobocyte) but all hematologists have not yet accepted the changes.

Cultures of bone marrow cells were used by Osgood⁴⁹¹ to determine the method of action of sulfanilamide. The drug had no effect on phagocytosis but appeared to neutralize the toxins of beta hemolytic streptococci.

Huggins and Smith⁴⁹² found that intravenous injections of colloidal thorium dioxide caused no significant changes in the cellular elements of venous blood. Thorium was fixed by the cells of the reticuloendothelial system. Anemia or plethora did not cause migration of the cells, and in newly formed marrow the macrophages were free from thorium. Growth in the thickness of the bone marrow occurs at its circumference.

Fitz-Hugh,⁴⁹³ in summarizing the action of certain drugs on the blood and bone marrow, noted reports of aplastic anemia (I), hemolytic anemia (II), thrombopenic purpura (III), agranulocytic angina (IV)

486 Wynkoop, E J, and Hadley, L. Schuller-Christian's Disease. Report of a Case, *Arch Pediat* **55** 417, 1938

487 Hankey, G T. Three Unusual Affections of the Jaw. Fibro-Myxo-Sarcoma of the Mandible, Multilocular Cyst Arising from Maxillary Dental Cyst, Xanthomatosis or Lipoid Granulomatosis of the Mandible (Schuller-Christian's Syndrome), *Proc Roy Soc Med* **31** 1137, 1938

488 Weil, P E, and Perles, S. La ponction sternale. Procédé de diagnostic cytologique, Paris, Masson & Cie, 1938

489 Reiter, B. Anatomische Untersuchungen zur Frage der Inhomogenität des Knochenmarkes im Hinblick auf die Auswertung der Sternalpunktion, *Ztschr f d ges exper Med* **103** 694, 1938

490 Osgood, E E. The Histogenesis, Classification and Identification of the Cells of the Blood and Marrow Based on Cultures and Hematologic Studies of Human Marrow and Blood, *Am J Clin Path* **8** 59, 1938

491 Osgood, E E. Culture of Human Marrow. Studies on the Mode of Action of Sulfanilamide, *J A M A* **110** 349 (Jan 29) 1938

492 Huggins, C, and Smith, K M. The Effect of Hypertrophic Cartilage on Bone Marrow Growth, *J Exper Med* **67** 41, 1938

493 Fitz-Hugh, T. Sensitivity Reactions of the Blood and Bone Marrow to Certain Drugs, *J A M A* **111** 1643 (Oct 29) 1938

and leukemoid reactions (V) after the use of the following substances ⁴⁹⁴ acetanilid (II), aminopyrine (II to V), antipyrine (II), arsphenamine (I to V), benzene (I to V), bismuth (III, IV), causalin (IV), cinchophen dinitrophenol (IV), ergot (III), gold salts (I, III, IV), neostibosan (IV), nirvanol (IV), novaldin (IV), acetophenetidin (IV), plasmochin (IV), quinine (II to V), sedoimid (III) and sulfanilamide (I to V)

Bock and Frenzel ⁴⁹⁵ ligated the splenic vein in 5 rabbits and produced inhibition of the bone marrow. The erythrocytes returned to normal in ten weeks, but the leukocytes did not do so until thirty-five weeks had passed and only after treatment had been given. Holderlin ⁴⁹⁶ injected into rabbits a 5 per cent sterile solution of milk casein, *Bacillus coli* vaccine, horse serum and histamine at intervals of three to four days. When the animals were sensitized, an injection was given and the bone marrow examined three to five days later. Some specimens showed "irritation" and others exhaustion. Serum was most toxic and milk casein and histamine the least. There appeared to be no parallelism between the condition in the bone marrow and the picture of the peripheral leukocytes.

Rhoads and Miller ⁴⁹⁷ studied 69 patients with idiopathic progressive anemia and found that the sternal bone marrow suggested a pentavalent classification. The first group showed replacement of hemopoietic tissue by a cellular structure composed of megakaryocytes in various stages of development. In the second group the marrow was sclerotic. The remaining three groups showed various degrees of cellularity of the marrow, aplastic, active and hyperplastic. In the latter groups there was failure of the hemopoietic cells to mature beyond an early undifferentiated stage. A relation to agranulocytosis was postulated.

After roentgen therapy, Meller, Gottlieb and Brauner ⁴⁹⁸ found, by means of repeated sternal punctures, that there is an excitation of the young elements of the bone marrow during the first few hours, with subsequent maturation. There is a considerable increase of adult granulocytic elements (segmented polymorphonuclear neutrophils). The increase in 1 case was from 284 per thousand to 628 per thousand.

⁴⁹⁴ The roman numerals after the names of the drugs refer to the diseases that have just been listed.

⁴⁹⁵ Bock, H. E., and Frenzel, B. Splenogene Knochenmarkshemmung. Tierexperimentellen Beweis, *Klin. Wchnschr.* **17** 1315, 1938.

⁴⁹⁶ Holderlin, H. Knochenmark und Blutbild beim sensibilisierten Tier, *Virchows Arch. f. path. Anat.* **302** 118, 1938.

⁴⁹⁷ Rhoads, C. P., and Miller, D. K. Histology of the Bone Marrow in Aplastic Anemia, *Arch. Path.* **26** 648 (Sept.) 1938.

⁴⁹⁸ Meller, O., Gottlieb, F., and Brauner, R. The Importance of the Indications from Sternal Puncture in Roentgen Therapy, *Radiology* **31** 149, 1938.

twenty-four hours after irradiation. The authors feel that the myelogram is a valuable guide during the course of roentgen therapy.

In 13 cases of multiple myeloma, Rosenthal and Vogel⁴⁹⁹ found no characteristic blood picture. Thrombocytopenia was present in 5 cases. In myelocytic myeloma, myelocytes and myeloblasts appeared in the blood stream. While roentgen observations, hyperproteinemia, the "formol gel" reaction and Bence Jones proteinuria were of diagnostic aid in some cases, the finding of myeloma cells on sternal puncture revealed the underlying condition.

HEMATOLOGIC METHODS

The time of erythrocyte regeneration after hemorrhage from peptic ulcer is constant according to Schrødt⁵⁰⁰ being thirty-three days. The rate of increase varies with the level of the red blood cell count after hemorrhage ceases, but the rate of production is always that normally required for balance. The rate of destruction is decreased in proportion to the amount of blood lost, since old as well as young cells are removed by bleeding and the new cells entering the circulation are not ripe for destruction.

Ettori and Grangaud⁵⁰¹ have modified the Ponder and Saslow method of estimating the total cell volume which depends on determination of the concentration of a known quantity of free hemoglobin added to a known volume of whole blood. Their values for normal subjects varied between 40 and 50 per cent, with an error said to have been within 1 per cent.

Studies of the blood volume have been reported by Gibson and his associates,⁵⁰² employing the azo dye Evans blue, the spectrophotometer and the Evelyn photoelectric microcolorimeter. The method was said to give constant values for plasma volume within a range of plus or minus 2.5 per cent. For clinical research the microcolorimeter was preferred by the authors to the spectrophotometer, because of its relative simplicity, speed, economy and absence of subjective error. An analysis of colorimetric methods of obtaining plasma volume determinations was

499 Rosenthal, N., and Vogel, P. Value of the Sternal Puncture in the Diagnosis of Multiple Myeloma, *J Mt Sinai Hosp* **4** 1001, 1938.

500 Schrødt, E. A Standard for Estimating Blood Regeneration After Hemorrhage, *Acta med Scandinav*, 1938, supp 89, p 157.

501 Ettori, J., and Grangaud, R. Sur la détermination du volume globulaire influence des anticoagulants sur le volume globulaire mesure par photométric, *Compt rend Soc de biol* **128** 181, 1938.

502 Gibson, J. G., Jr., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J Clin Investigation* **16** 301, 1937. Gibson, J. G., Jr., and Evelyn, K. A. Clinical Studies of the Blood Volume. Adaptation of the Method to the Photoelectric Microcolorimeter, *ibid* **17** 153, 1938. Thomson, Hirsheimer, Gibson and Evans¹⁶⁴

published by Gregersen ⁵⁰³ He criticized, on grounds of inaccuracy, the ordinary dye and colorimetric methods and advocated the use of the blue dye T-1824, with spectrophotometric determinations

A calibrated micropipet with a 50 cubic millimeter capacity has been devised by Kato ⁵⁰⁴ It is adapted for small quantities of blood and is applicable to a number of hematologic procedures, including determinations of the sedimentation rate and the volume of packed cells and micro-precipitation tests for syphilis

A number of papers dealing with the factors influencing sedimentation of erythrocytes and questioning methods of so-called correction of the rate for changes in cell volume have been published during the past year Tiffeneau and Gysin ⁵⁰⁵ separated plasma, by ultrafiltration, into two fractions The rate of settling of the red blood cells was decreased in the nonprotein fraction, whereas it was increased in the protein fraction In the case of specimens of blood possessing different sedimentation rates, the rates of settling become the same when the nonprotein plasma fractions are used but vary when the protein fractions are employed in accordance with the rates of the specimens from which the fractions were obtained On the other hand, the use of cells from different specimens of blood does not influence the rate The authors also concluded that plasma protein accelerates the sedimentation rate in accordance with its molecular size Schuster ⁵⁰⁶ reported his observations in 121 cases and found that polycythemia retards the sedimentation rate, whereas anemia accelerates it but that no charted system of correction for changes in the blood count is satisfactory He advocated adjustment of the count to a standard concentration by removal or addition of plasma Bouton, ⁵⁰⁷ however, stated, from his observations on patients after malaria inoculation that the relative number of erythrocytes in the plasma has a negligible effect per se on the rate of settling of the red blood cells and that such an effect as may exist is inconstant He concluded that attempts at compensation for anemia represent pseudoaccuracy and that the unmodified sedimentation curve, graphi-

503 Gregersen, M I An Analysis of Colorimetric Methods in Relation to Plasma Volume Determinations, *J Lab & Clin Med* **23** 423, 1938

504 Kato, K Combination Microhemopipette for Determination of the Sedimentation Rate, Packed Cell Volume and Fragility of Erythrocytes, Especially Adapted for Use in Children and Small Laboratory Animals, *J Lab & Clin Med* **23** 980, 1938

505 Tiffeneau, R, and Gysin O Role des protides plasmatiques dans la vitesse de sedimentation des hematies Influence du volume des molecules protidiques, *Compt rend Soc de biol* **126** 1160, 1937

506 Schuster, N H Sedimentation Rate in Relation to the Red Cell Count The Problem of Correction, *Tubercle* **19** 529, 1938

507 Bouton, S M, Jr Erythrocyte Sedimentation and Anemia A Preliminary Report, *J Lab & Clin Med* **23** 519, 1938

cally recorded, is a valuable diagnostic aid Hambleton and Christianson⁵⁰⁸ studied the sedimentation rate of blood adjusted with isotonic solution of sodium citrate to cell volumes of 25, 29, 35, 40 and 45 per cent Their results indicated to them that correction for the cell volume is, in general, of advantage for blood with a volume of packed cells in excess of 45 per cent but that correction was undesirable when the volume was subnormal Cutler, Park and Herr⁵⁰⁹ stated that anemia has little or nothing to do with the aggregation or sedimenting phase of the sedimentation phenomenon but that it is concerned with the terminal or packing phase Consequently, according to these authors, correction for anemia by charts or by adjustment of plasma to obtain a normal cell volume is inaccurate, and interpretation should be based on the shape of the sedimentation curve, as well as on the extent of the fall at one hour Hynes and Whitby,⁵¹⁰ on the other hand, have supported the principle of the Wintrobe and Landsberg method of correction of the sedimentation rate for anemia by means of a logarithmic chart but have put forward a new correction chart based on a wider range of rates than that employed by Wintrobe and Landsberg They advocated expressing the sedimentation rate in general terms rather than as an exact figure Observations of the sedimentation rate for children with nutritional anemia led Smith⁵¹¹ to conclude that the blood in these cases does not behave as does diluted normal blood A further report was published by Lee⁵¹² on an automatic photographic recorder of erythrocyte sedimentation

508 Hambleton, A, and Christianson, R A A Simplified Method of Correcting the Sedimentation Rate for the Effect of Cell Volume, *J Lab & Clin Med* **23** 860, 1938

509 Cutler, J W, Park, F R, and Herr, B S The Influence of Anemia on Blood Sedimentation, *Am J M Sc* **195** 734, 1938

510 Hynes, M, and Whitby, L E H Correction of the Sedimentation Rate for Anaemia, *Lancet* **2** 249, 1938

511 Smith, C H Sedimentation Rate in Nutritional Anemia of Infants and Children Its Response to Treatment with Iron (Ferrous Sulfate), *Am J Dis Child* **56** 510 (Sept) 1938

512 Lee, T The Sedimentometer A Photographic Recorder of the Suspension Stability of the Erythrocyte, *Am J M Sc* **195** 729, 1938

News and Comment

Biological Photographic Association—The ninth annual convention of the Biological Photographic Association will be held September 14 to 16 at the Mellon Institute for Industrial Research, Pittsburgh. The program will be of interest to scientific photographers, scientists who use photography as an aid in their work, teachers in the biologic fields, technical experts and serious amateurs. It will include discussions of motion picture and still photography, photomicrography, color and monochrome films and processing, all in the field of scientific illustrating. Up-to-date equipment will be shown in the technical exhibit, and the print salon will display the work of many of the leading biologic photographers in the United States and abroad.

The *Biological Photographic Association Journal* is published quarterly and constitutes a volume of about 250 pages, which is furnished free to members. Membership privileges include an authoritative question and answer service and the right to borrow loan albums and exhibits of scientific prints for study and display.

Further information about the association and the convention may be obtained by writing the secretary of the Biological Photographic Association, University Office, Elizabeth Steel Magee Hospital, Pittsburgh.

Book Reviews

Kvantitative urinsediments bestemmelser Et bidrag til belysning af proteinspørgsmaalet ved nefritisdiaten Bv Asger Naeraa Pp 191 Copenhagen Nyt Nordisk Forlag-Arnold Busck, 1936

The author gives in this book, or thesis, for which he was awarded the degree of Doctor of Medicine at the University of Copenhagen, an illustration of the effect of the protein diet in the treatment of nephritis He calls the work "Quantitative Determinations of Urinary Sediments"

In the introduction he mentions the three generally accepted types of Bright's disease, their characteristic symptoms being (1) hematuria, (2) albuminuria and (3) hypertension But it is on the classification made by Addis (hemorrhagic, degenerative and arteriosclerotic), with some modifications of his own, that he bases his clinical experiments With sediment counts he finds it possible to follow the course of inflammatory renal conditions from day to day

He soon found much uncertainty concerning the following phases of the problem of sediment counts (1) the fluctuation of the sediment contents under different normal physiologic conditions, (2) the quantity of sediment in persons with benign albuminuria and (3) the influence of the usual hospital medicaments, especially salicyl preparations

The first part of the book is devoted to the examination of these problems, the discussion of the organic components of the sediment and the description of the technic used by the author

The second part deals with the main issue, the significance of the diet during the treatment of acute hemorrhagic nephritis, with special reference to the possible injuriousness of protein Naeraa points out that the uncertainty in regard to the influence of the diet has caused most patients with acute nephritis to be kept on a general diet for a feverish condition and that a remarkable number of physicians still adhere to the slogan of Crestien "*Le lait ou la mort*" The result is that many patients suffer from undernourishment

After examination of many discussions of the problem, the author finds that the main reason for disagreement is that the writers do not keep its different phases separate He therefore classifies the main questions as follows (1) the possible injuriousness and irritating effect of protein during acute inflammation of the kidney, (2) the possible injurious effect of protein during chronic nephritis, especially arteriosclerotic nephritis, and (3) the possible injurious influence of protein when renal insufficiency is present, as shown by the nonprotein nitrogen of the blood The only one of these questions on which all agree is that protein must not be given during acute renal insufficiency

After a short review of the importance of the different symptoms, followed by an outline and diagrams of the course of hemorrhagic nephritis, the author describes his experiments with a number of patients Only males were selected, in order that urine free from other elements might be obtained He first gave 9 patients a diet of 2,750 calories, with a protein content of 40 Gm After the hematuria became constant a change was made to 3,000 calories, with 125 Gm of protein The two diets were thereafter given alternately, the period of each lasting from eight to nineteen days One patient was given the high protein diet only, and 3 were kept on the usual low protein nephritic diet Daily counts of the urinary sediments were kept in all cases The description of each of the experiments is illustrated by graphs and tables, and an abstract of each case is printed at the end of the book

In conclusion, Naeraa gives the following summary of his studies and experiments

1 The Addis method of counting the number of cells and casts in the urine, as well as the author's modification of it, gives a true estimate of these elements

2 When the urine has been separated and Quensel's color fluid added, the formed elements (if the urine is concentrated) will keep for several days

3 Sediment determinations for 70 apparently well persons aged from 20 to 40 gave the following values for twelve hour night urine

Erythrocytes	Leukocytes and Epithelial Cells	Casts
0 1,100,000	48,000 4,000,000	0 8,700
130,000	1,000,000	1,900

All casts were hyaline

In the case of 10 persons aged from 55 to 90 the sediment deviated from normal. Casts were found in great number, up to 15,000

4 Examination of the day urine from 21 of the 70 persons mentioned did not show any difference in the amount of formed elements from that of the night urine. The nephritic patients gave indication of greater bleeding during the day than at night

5 Examination of the sediments from normal persons exposed to great exertion gave no indication of any exertion hematuria. On the other hand, the number of casts may rise as high as that found in patients with nephritis. All casts are hyaline, even though the precipitation of crystals may give them a deceptive resemblance to granular casts. The number of casts seems to increase with the duration of the exertion

6 Salicyl preparations, even in ordinary therapeutic doses, will cause an increase in the number of casts. After only 1 Gm of magnyl has been given there may be as many as 50,000 casts in twelve hour night urine. After a salicylate has been taken daily for a longer time, this number may increase to several hundred thousand. The casts are all hyaline. It is presumed that the casts increase in number because the salicyl radical disengages the protein substance normally contained in the urine. There is no indication that salicyl preparations damage the kidneys

7 Examination of the night and day urine of 11 boys with benign albuminuria showed that the sediment did not contain an abnormal number of erythrocytes or leukocytes, but that off and on the number of hyaline casts was increased

8 The highest recorded number of erythrocytes found in the night urine during the acute stage of hemorrhagic nephritis is 10,000,000,000, which means about 2 cc of blood

During the acute stage of hemorrhagic nephritis the patients have real pyuria. Sometimes they secrete as many white as red blood corpuscles

10 A graph for sediment counts carried out daily during the course of hemorrhagic nephritis shows great fluctuation in the number of erythrocytes, even when they are decreasing. The white corpuscles, on the other hand, show less fluctuation. Great increase of erythrocytes is often seen, but does not mean any aggravation of the process. An increase of the white blood corpuscles accompanies aggravation. The activity of the renal inflammation ought therefore always to be estimated from the number of leukocytes and epithelial cells in the urine, and not from the degree of hematuria

11 The number of casts during the course of hemorrhagic nephritis varies, yet this is not a measuring stick of renal inflammation. The number of hyaline casts, on the other hand, is always in a certain proportion to the degree of albuminuria

12 Hyaline casts may be formed as soon as the urine is sufficiently concentrated. The proteins which appear in the urine under normal circumstances will

be disengaged at the isoelectric point. This disengagement takes place where the urine is concentrated by retrograde resorption, namely, in the tubules where the casts are formed.

13 General clinical impressions, laboratory examinations and daily sediment counts made on patients with hemorrhagic nephritis who have received diets alternately poor and rich in proteins have not indicated that a diet rich in meat has damaged the kidney.

The general impression during the experiments was that the renal disease seemed to improve with food rich in proteins.

This monograph contains a large store of information concerning the significance of sediment counts of the urine and the influence of various factors on them. The careful study of the course of patients with nephritis requires some method of measuring the inflammation in the kidney. A study of the problem as outlined by Naeraa is desirable and profitable.

The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds By Perrin H. Long, M.D., Associate Professor of Medicine, The Johns Hopkins University, and Eleanor A. Bliss, Sc.D., Fellow in Medicine, The School of Medicine, The Johns Hopkins University. Price, \$3.50. Pp. VII + 319, with 6 charts. New York: The Macmillan Company, 1939.

The entire medical profession is indebted to the authors of this monograph. For in it Drs. Long and Bliss have presented a clear and interesting statement of current opinion regarding the clinical usefulness of sulfanilamide and allied compounds. Their own knowledge of the subject is, of course, authoritative.

The book represents an amazing bit of work, for it must have been written during a time when the authors were under great pressure when new knowledge was coming to light almost every day and when current literature, which had to be read and sifted critically, was growing with prodigious speed. Evidently the authors have felt a strong sense of responsibility for making the information which they have released as recent as possible. The first printing appeared in June, and yet a special addendum was inserted so late as April 25, and the preface was written on February 14. The book, therefore, is as up-to-date as they could make it.

It begins with a delightfully written chapter giving the history of sulfanilamide therapy. Then follow seven chapters which deal with the chemotherapy of experimental bacterial infections, the comparative pharmacology of sulfanilamide and allied compounds, the mode of action of these drugs, their clinical use and, finally, their clinical toxic manifestations. At the end of each chapter is a bibliography, toward the end of the book, an index of authors, and at last, an unusually complete subject index.

The part of the volume which deals with clinical treatment will appeal most to practicing physicians. The authors show admirable restraint and take care to be conservative rather than too enthusiastic. They mention the variety of diseases which are being treated with sulfanilamide, the customary dose of the drug in common use and the therapeutic results which seemingly have been obtained in their own experience or in that of others.

They discuss debatable matters in connection with sulfanilamide therapy frankly and with open mind, they point out gaps in present knowledge, they look to the future. Not only do they make any reader sense the importance of the discovery of sulfanilamide and explain how he may use the drug or its allied compounds with reasonable intelligence, but they stimulate imagination by suggesting the diverse ways by which, in the future, chemotherapy is likely to become increasingly significant. On the whole, the book is one of the most important books of the year. Every physician should read it.

EFFECT OF DIHYDROTACHYSTEROL IN TREATMENT OF PARATHYROID DEFICIENCY

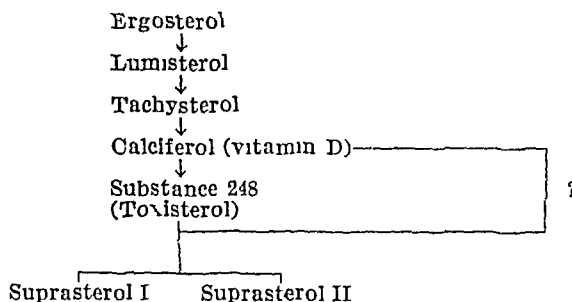
EDWARD ROSE, M D

AND

F WILLIAM SUNDERMAN, M D, P H D

PHILADELPHIA

Tachysterol is one of several sterols derived from ergosterol by irradiation with ultraviolet light. Its relation to the other sterols can best be illustrated by the scheme modified by Bills¹ from that of Setz



Experimentally tachysterol has been found to cause an increase in absorption and urinary excretion of calcium, and a rise in the concentration of calcium in the serum. There is no evidence that parathyroid function is affected. An orally effective derivative, dihydrotachysterol (antitetanic preparation no 10, or "A T 10"), was first used in the treatment of parathyroid tetany by Holtz,² in Germany, in 1933. Since then it has been extensively used, chiefly in Germany, and its effects have been reported on in considerable detail. The literature has recently been reviewed by Albright and his associates.³ From

From the William Pepper Laboratory of Clinical Medicine, the Endocrine Section of the Medical Clinic and the Department of Research Medicine, Hospital of the University of Pennsylvania

1 Bills, C E. The Chemistry of Vitamin D, J A M A **110** 2150 (June 25) 1938

2 Holtz, F. Die Behandlung der postoperativen Tetanie, Arch f klin Chir **177** 32, 1933

3 Albright, F, Bloomberg, E, Drake, T, and Sulkowitch, H W. A Comparison of the Effects of A T 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, J Clin Investigation **17** 317, 1938

their review the principal data concerning dihydrotachysterol may be summarized

Most writers agree that dihydrotachysterol has no antirachitic effect. The chief effects noted have been increase in the concentration of serum calcium and decrease in the concentration of inorganic serum phosphorus. The urinary calcium has been found to be increased and the fecal calcium decreased. Both the ionized and the protein-bound fraction of the serum calcium have been reported to be increased, with a more marked effect on the ionized fraction in cases of tetany. Holtz, Gissel and Rossmann⁴ concluded that the calcium bound by protein was the first to become increased, with a subsequent increase in the diffusible fraction. (Their conclusions, however, do not appear to be tenable, for reasons which will be referred to later.) If the calcium intake is low, the increase in serum calcium is effected by withdrawal of calcium from the skeletal stores. No detailed studies of the effect of dihydrotachysterol on calcium and phosphorus metabolism appear to have been made prior to those reported by Albright and his associates.³ They compared the effects of vitamin D, dihydrotachysterol and parathyroid extract (solution of parathyroid) in 3 cases of hypoparathyroidism and concluded that the fundamental actions of vitamin D and dihydrotachysterol are similar—an increased absorption of calcium from the intestine and an increased excretion of phosphorus in the urine, the ratio of the latter to the former being greater with dihydrotachysterol. They concluded that the effect of dihydrotachysterol on the concentrations of calcium and phosphorus in the serum is secondary to these fundamental actions. Their observations indicate that the action of vitamin D is slower in onset and more prolonged than that of dihydrotachysterol.

Excessive doses of dihydrotachysterol may produce fatal intoxication with hypercalcemia and extensive calcification, especially in the urinary tract, where calculi may occur. The preparation used clinically is a 0.5 per cent solution of dihydrotachysterol in sesame oil. It is administered orally. The optimal dose varies widely, depending on the severity of symptoms and the degree of hypocalcemia. An initial dose of 5 to 10 cc daily for three or four days usually results in a marked rise in concentration of serum calcium in from three to nine days after the first dose is given—much larger doses are occasionally necessary, however. The maintenance dose is usually between 2 and 6 cc weekly in cases of mild involvement. There is a cumulative effect, and periodic determinations of the serum calcium are essential to avoid dangerous hypercalcemia. There is no evidence of harmful effect from prolonged administration of the substance in proper doses. The requirement is increased during menstruation, pregnancy and periods of great physical

⁴ Holtz, F., Gissel, H., and Rossmann, E. Experimentelle und klinische Studien zur Behandlung der postoperativen Tetanie mit A.T. 10. *Deutsche Zeitschrift für Chirurgie* **242**: 521, 1934.

on emotional activity. Castration by 1000 röntgen irradiation is said to decrease the requirement in women. The action of dihydrotachysterol is said to be antagonized by estrogen and androgen. Lenticular cataract, a common complication of parathyroid deficiency, is said to be prevented by dihydrotachysterol but not to be affected once it has begun.

Dihydrotachysterol has been shown to be highly effective in controlling and preventing the manifestations of parathyroid deficiency: a large number of cases in which it was successfully used having been reported, chiefly in the German literature.⁵ MacBryde,⁶ Arnold and Blum⁷ and Swinton⁸ have recently reported on its use in the United States. It has also been used in the management of a number of other conditions—the tetany of sprue, asthma, urticaria, hemophilia, impetigo herpetiformis and a variety of peripheral circulatory disturbances. At present the chief advantages of the drug in treating parathyroid tetany appear to be (1) its prompt and continued efficacy by peroral administration in maintaining normal concentrations of serum calcium and controlling symptoms without the necessity of dietary restriction (low phosphorus diet) or adjuvant therapy (calcium or vitamin D), and (2) the small maintenance dose usually necessary. The principal objections to its use appear to be (1) its cost and (2) the necessity of guarding against hypercalcemia.

We wish to report the effects of dihydrotachysterol on 5 patients with parathyroid deficiency following thyroidectomy and ranging from five months to thirteen years in duration. The method of study in general followed the plan described by Bauer and Aub.⁹ The patients were given a diet the calcium content of which was approximately 1 Gm daily. All rejected food was weighed and the calcium content calculated.

The total period of study was divided into periods of three days as follows: (a) two to four periods during which the patient continued to receive the medication previously necessary to control symptoms (one of our patients, M. R., had received no previous therapy), (b) two

5 Symposium. Die Tetanie (Nebenschilddrüseninsuffizienz) und ihre Behandlung, *Med Klin* **32** 656, 1936. Martini, P., and Heymer, A. Beitrag zur Behandlung der postoperativen Tetanie mit dem antitetanischen Präparat 10 (A. T. 10-Holtz), *München med Wchnschr* **80** 1864, 1933. Winterstein, O. Zur Behandlung schwerer und leichter Tetanien mit A. T. 10, *Deutsche med Wchnschr* **60** 1831, 1934.

6 MacBryde, C. M. The Treatment of Parathyroid Tetany with Dihydrotachysterol, *J. A. M. A.* **111** 304 (July 23) 1938.

7 Arnold, C. H., and Blum, H. The Control of Hypoparathyroidism, *West J. Surg.* **44** 546, 1936.

8 Swinton, N. W. Postoperative Parathyroid Tetany, *New England J. Med.* **217** 165, 1937.

9 Bauer, W., and Aub, J. C. Studies of Inorganic Salt Metabolism. I. The Ward Routine and Methods, *J. Am. Dietet. A.* **3** 106, 1927.

periods during which all medication was omitted, (c) one period during which dihydrotachysterol was given alone in doses of 10 cc daily, and (d) one to five periods during which dihydrotachysterol was given alone in doses of 2 cc daily. One patient (L. H.) received viosterol alone in doses of 2 cc daily for two periods prior to the administration of dihydrotachysterol. A greater number of control periods without calcium or viosterol therapy would have been desirable (except in the case of M. R., who had received no such therapy). However, the 4 patients who had received this therapy had such severe parathyroprival symptoms that they could not safely be carried longer than for two periods (six days) without treatment. All urine and feces were collected for each period, the limit of the periods for collection of feces being determined by the appearance of carmine in the stools.

Determinations at the end of each period were made of the following: the total of serum calcium, by the method of Clark and Collip,¹⁰ the diffusible fraction of serum calcium, from ultrafiltrates of serum obtained through collodion sacks according to a modification of the method of Greenberg and Gunther,¹¹ the inorganic phosphorus of the serum, by the method of Fiske and Subbarow,¹² the total serum protein, and the calcium contents of the urine and feces, which were pooled for each period. The calcium of the urine and that of the feces were measured by modifications of the methods of Shohl and Pedley¹³ and McCrudden,¹⁴ respectively.

REPORT OF CASES

CASE 1—L. H., an unmarried white woman aged 44, underwent a subtotal thyroidectomy for hyperthyroidism in another hospital in 1923. This was followed by bilateral paralysis of the recurrent laryngeal nerves, necessitating a tracheotomy, and by severe symptoms of parathyroid deficiency. The patient was first seen by us in 1927, at which time bilateral lenticular opacities were found. There has been little change in these. The patient has been under continuous observation since 1927. Two parathyroid transplants were made in 1928,

10 Clark, E. P., and Collip, J. B. The Tisdall Method for Determination of Blood Serum Calcium, with a Suggested Modification, *J Biol Chem* **63** 461, 1925.

11 Greenberg, D. M., and Gunther, L. On the Determination of Diffusible and Nondiffusible Serum Calcium, *J Biol Chem* **85** 491, 1930.

12 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J Biol Chem* **66** 375, 1925.

13 Shohl, A. T., and Pedley, F. G. A Rapid and Accurate Method for Calcium in the Urine, *J Biol Chem* **50** 527, 1922.

14 McCrudden, F. H. The Quantitative Separation of Calcium and Magnesium in the Presence of Phosphates and Small Amounts of Iron, Devised Especially for the Analysis of Foods, Urine and Feces, *J Biol Chem* **7** 83, 1909, The Determination of Calcium in the Presence of Magnesium and Phosphates, the Determination of Calcium in the Urine, *ibid* **10** 187, 1911.

with little benefit. Therapy had included large doses of calcium, vitamin D, parathyroid extract (solution of parathyroid), desiccated thyroid and a diet low in phosphorus. The patient had become anemic, and electrocardiographic evidence of myocardial damage had appeared. Dihydratichysterol was given from March 27 to Sept 17, 1937, with resulting improvement. From September 17 to November 8, she received 15 teaspoonfuls of calcium lactate and 10 minims (0.62 cc) of viosterol daily with a low phosphorus intake. Her symptoms were only partially controlled by this therapy. She was under observation in the hospital from November 8 to December 9, 1937. Since that time she has remained under observation in the outpatient clinic and has been kept fairly comfortable by large doses of calcium lactate combined with small doses of dihydratichysterol (adequate doses of the latter were not possible because of the cost). The potency of dihydratichysterol is illustrated by the fact that the patient showed severe symptoms of intoxication

TABLE 1—*Record of Patient L. H.*

Date	Total Calcium, Mg per Cc	Diffusible Calcium, Mg per Cc	Inorganic Phosphorus, Mg per Cc	Serum Protein, Gm per Cc	Comment
11/12/37	8.4		4.4	7.2	Calcium lactate and viosterol
11/20/37	5.7	2.7	5.0	5.6	Viosterol only for 5 days, marked symptoms of parathyroid deficiency
11/23/37	5.8				All medication withdrawn, severe symptoms
11/26/37	5.3	2.5	5.7	5.4	Dihydratichysterol begun 11/27/37
11/29/37	6.4				(10 cc daily)
12/ 2/37	8.4	3.8	4.9	6.0	Marked clinical improvement, 34 cc dihydratichysterol to date
12/ 6/37	9.2	4.3	4.0	5.9	Dihydratichysterol, 2 cc daily
12/ 9/37	8.6				Dihydratichysterol, 2 cc every other day, left hospital
12/20/37	8.9				Dihydratichysterol, 2 cc every other day
1/ 5/38	8.3				Calcium lactate added
1/21/38	7.8				
4/29/38	10.2				Severe symptoms of hypercalcemia
7/12/38	15.7		3.1		
9/15/38	9.8		3.9		

(vertigo, tinnitus, thirst, polyuria, nausea and abdominal cramps), with a rise of total serum calcium to 15.7 mg per hundred cubic centimeters, after taking 8 teaspoonfuls of calcium lactate and 2 cc of dihydratichysterol daily from June 12 to July 8. The significant data relating to this patient are shown in table 1.

CASE 2—J. J., a married mulatto woman aged 38, underwent a subtotal thyroidectomy for hyperthyroidism in another hospital in 1927. Severe symptoms of parathyroid deficiency, including convulsive seizures, began several months later and continued intermittently until we first saw the patient, in 1935. At this time there was evidence of mild recurrent hyperthyroidism and bilateral cataracts. There was a questionable history of syphilitic choroiditis. Since first entering this clinic, the patient had received calcium lactate, viosterol, parathyroid extract, a low phosphorus diet and intermittent iodine therapy. At the time of admission to the hospital she was taking 16 teaspoonfuls of calcium lactate and 10 minims of viosterol daily, with only partial relief of symptoms. She was studied in the hospital from Sept 8 to 30, 1937. Subsequently she was under observation in

the outpatient clinic Dihydrotachysterol was omitted from Jan 14 to Oct 13, 1938, because she could not afford it During this period her general condition was about as it was before dihydrotachysterol therapy was started, and a convulsion occurred in September, despite a diet low in phosphorus and administration of 15 teaspoonfuls of calcium lactate daily After the resumption of dihydrotachysterol the symptoms disappeared within four days, and the total serum calcium rose to a normal level The cataracts progressed The significant data relating to this case are shown in table 2

CASE 3—H E, a white man aged 40, underwent a partial thyroidectomy for nontoxic nodular goiter in another hospital in 1918 This was followed immediately by parathyroid tetany, which was manifested by intermittent syncopal attacks or convulsive seizures until the patient was first seen by us, in April 1937

TABLE 2—Record of Patient J J

Date	Total Calcium, Mg per Cc	Diffusible Calcium, Mg per Cc	Inorganic Phosphorus, Mg per Cc	Serum Protein, Gm per Cc	Comment
9/13/37	8.3	4.3	3.9	7.5	Vioosterol and calcium lactate
9/17/37	6.5				Therapy stopped 9/15/37, severe tetany
9/20/37	5.6	2.6	5.0	7.1	Symptoms increasingly severe
9/21/37	5.5				Dihydrotachysterol 9/21 to 9/24/37 (10 cc daily)
9/24/37	6.4				Clinical improvement, dihydro tachysterol, 2 cc daily
9/26/37	9.2	3.7	4.2	7.7	No symptoms
9/29/37	9.4	4.4	4.0	7.1	Discharged 9/30/37, dihydrotachysterol reduced to 2 cc twice weekly unrestricted diet
10/ 9/37	9.3				
11/26/37	8.0				Minimal symptoms, dihydrotachysterol, 2 cc twice weekly
12/15/37	7.6				Dihydrotachysterol increased to 3 cc twice weekly 11/30/37, discontinued 1/14/38
3/21/38	9.1				
4/19/38	7.7				
9/20/38	8.2		3.8		Convulsion 9/21/38, symptoms only partially controlled
10/17/38	9.7		4.0		On 10/13 1 cc dihydrotachysterol every other day added to 10 tea spoonfuls of calcium lactate daily no symptoms at time of writing

At this time the concentration of calcium was 5.6 mg and that of inorganic phosphorus 5.5 mg per hundred cubic centimeters of serum There was no evidence of lenticular cataract The symptoms were partially controlled by 6 teaspoonfuls of calcium gluconate daily The patient was under observation in the hospital from Dec 6 to 26, 1937 Since that time he has been followed in the outpatient clinic He has remained free from symptoms, although the concentration of serum calcium has remained slightly below the normal level with 2 cc of dihydrotachysterol twice a week and no other medication or restriction of diet The significant data relating to this case are shown in table 3

CASE 4—M H, a married white woman aged 30, underwent a partial thyroidectomy for nontoxic nodular goiter in another hospital in 1935 Symptoms of parathyroid deficiency developed immediately, with occasional convulsions There was also evidence of hypothyroidism Therapy had included small doses of calcium lactate, parathyroid extract (solution of parathyroid) and desiccated thyroid She was first seen by us on Feb 4, 1938, when the concentration of serum calcium was 7.5 mg per hundred cubic centimeters She was under observation in

the hospital from February 7 to March 5. A parathyroid transplant was made on March 18, subsequent observations indicated that this was without effect. The patient has remained under observation in the outpatient clinic since leaving the hospital. She has remained free from symptoms and without evidence of cataract.

TABLE 3—*Record of Patient H E*

Date	Total Calcium, Mg per Cc	Diffusible Calcium, Mg per Cc	Inorganic Phosphorus, Mg per Cc	Serum Protein, Gm per Cc	Comment
12/13/37	7.8	3.2	5.5	7.1	Calcium lactate
12/16/37	6.9				Calcium withdrawn 12/14/37
12/20/37	6.8	3.0	5.9	7.6	
12/22/37	7.7				Dihydrotachysterol started (10 cc daily for 3 days, thereafter 2 cc daily), mild symptoms of parathyroid deficiency
12/25/37	10.3	4.0	4.9	7.3	No symptoms, discharged 12/26/37
1/21/38	9.0		4.5		No symptoms, 2 cc dihydrotachysterol twice weekly
2/4/38	9.4		4.7		No symptoms, 2 cc dihydrotachysterol twice weekly
3/18/38	8.5		4.0		No symptoms, 2 cc dihydrotachysterol twice weekly
4/20/38	8.3		4.7		No symptoms, 2 cc dihydrotachysterol twice weekly
7/15/38	8.6				No symptoms, 2 cc dihydrotachysterol twice weekly
10/28/38	7.4		4.4		Dihydrotachysterol omitted for 2 weeks, then resumed for 4 days prior to determination, no symptoms

TABLE 4—*Record of Patient M H*

Date	Total Calcium, Mg per Cc	Diffusible Calcium, Mg per Cc	Inorganic Phosphorus, Mg per Cc	Serum Protein, Gm per Cc	Comment
2/13/38	7.5	3.2	4.8	6.8	Tetany of moderate severity, calcium lactate plus viosterol
2/16/38	6.2				Tetany more marked, no medication
2/19/38	5.7	2.6	5.5	6.5	Tetany no medication
2/22/38	7.0				10 cc dihydrotachysterol daily 2/20 to 2/23/38
2/25/38	9.5	4.2	3.7	6.9	2 cc dihydrotachysterol daily 2/23 to 2/27/38, marked improvement
3/3/38	9.1		4.1		2 cc dihydrotachysterol every other day 2/27 to 3/5/38, left hospital 3/5/38
5/10/38	8.9		3.4		2 cc dihydrotachysterol 3 times a week, no symptoms
6/11/38	9.1		3.8		2 cc dihydrotachysterol 3 times a week
6/24/38	7.5		4.5		Dihydrotachysterol stopped 6/11/38, recurrence of symptoms
7/22/38	8.5		3.5		Dihydrotachysterol resumed (2 cc twice a week) 7/4/38
10/14/38	10.1		3.5		No symptoms, 2 cc dihydrotachysterol twice weekly

under treatment with 2 cc of dihydrotachysterol two or three times a week. This medication was stopped from June 11 to July 4 to permit evaluation of the parathyroid transplant, there was a fall in the concentration of serum calcium and recurrence of symptoms at this time. The significant data relating to this case are shown in table 4.

CASE 5—M R, a married white woman aged 30, was first seen in the outpatient clinic in July 1937, at which time a diagnosis of toxic diffuse goiter was

made A subtotal thyroidectomy was done in this hospital on August 20 The postoperative convalescence was without incident The patient was not seen by us after her discharge until Jan 5, 1938, when she presented evidence of parathyroid deficiency, the concentration of serum calcium at this time was 6.3 mg per hundred cubic centimeters She was studied in the hospital from January 14 to February 11 She has received no dihydrotachysterol since leaving the hospital but has continued on a low phosphorus diet, with varying doses of desiccated thyroid and calcium lactate At the time of writing (November 1938) the concentration of serum calcium was normal (9 mg per hundred cubic centimeters), three weeks after calcium lactate was stopped The significant data relating to this case are shown in table 5

COMMENT

Our experience confirms the previous reports of the effectiveness of dihydrotachysterol in relieving the symptoms of parathyroid deficiency

TABLE 5—*Record of Patient M R*

Date	Total Calcium, Mg per Cc	Diffusible Calcium, Mg per Cc	Inorganic Phosphorus, Mg per Cc	Serum Protein, Gm per Cc	Comment
1/18/38	6.1	2.3	6.7	7.5	No therapy, moderate symptoms of tetany
1/21/38	6.0		6.7		No therapy, moderate symptoms of tetany
1/24/38	6.5				10 cc dihydrotachysterol daily 1/22 to 1/24/38
1/27/38	7.6		6.1	7.1	2 cc dihydrotachysterol daily 1/25 to 2/8/38, gradual improvement in symptoms
1/30/38	7.8	3.4	6.4	7.2	2 cc dihydrotachysterol daily
2/ 2/38	8.4				2 cc dihydrotachysterol daily
2/ 5/38	8.6	3.7	5.8	7.4	2 cc dihydrotachysterol daily
2/ 8/38	8.7				Dihydrotachysterol stopped
2/ 9/38	9.0	3.4	5.4	7.7	Almost no symptoms, left hospital 2/11/38
11/ 8/38	10.6		4.2		No dihydrotachysterol since 2/11/38, no calcium since 10/4/38, no evidence of tetany

and increasing the concentration of serum calcium The danger of producing toxic symptoms and hypercalcemia is indicated by our experience with patient L H It should be emphasized again that the severity of symptoms in 4 of our patients precluded the possibility of longer periods of observation without therapy In 4 of our patients the response to dihydrotachysterol was relatively prompt, the concentration of total serum calcium returned to normal, with corresponding relief of symptoms, in from four to nine days after the beginning of treatment The fifth patient (M R) had received no previous treatment and presented relatively mild symptoms, she showed a slow, progressive increase in concentration of serum calcium, with corresponding gradual clinical improvement, over a period of eighteen days during which she received doses of dihydrotachysterol identical with those given the other patients

Our experience also confirms previous observations as to the lack of correlation between the degree of hypocalcemia and the severity of symptoms. The case of patient H E illustrates this fact particularly, his symptoms, which were largely episodic, were often absent when the concentration of serum calcium was decreased (7.4 mg per hundred cubic centimeters). Patient J J, on the other hand, had a generalized convulsion the day after the concentration of serum calcium was determined to be 8.2 mg per hundred cubic centimeters.

In table 6 are given the results of the fractionations of the serum calcium. The total calcium in the serum was calculated in terms of millimols per kilogram of water by means of the conversion factors

TABLE 6—*Summary of Studies of Serum Calcium*

Subject	Date	Specific Gravity, 20 C/20 C	Total Calcium, mM/Kg H ₂ O	Diffusible Calcium, mM/Kg H ₂ O	Ca++ (Calculated), mM/Kg H ₂ O	Nondiffusible Calcium, mM/Kg H ₂ O	Diffusible Calcium-Ca++ Ratio	Diffusible Calcium Total Calcium Ratio
J J	9/10	1.0287	2.22	1.08	1.00	1.14	1.08	0.49
	9/20	1.0276	1.49	0.65	0.61	0.84	1.07	0.44
	9/26	1.0294	2.47	0.93	1.00	1.54	0.93	0.38
	9/29	1.0277	2.51	1.11	1.10	1.40	1.00	0.44
L H	11/14	1.0279	2.25		0.97			
	11/20	1.0232	1.51	0.68	0.65	0.83	1.05	0.45
	11/26	1.0228	1.40	0.63	0.70	0.77	0.90	0.45
	12/2	1.0245	2.23	0.95	1.09	1.28	0.97	0.43
	12/6	1.0241	2.44	1.08	1.20	1.36	0.90	0.44
H E	12/13	1.0276	2.09	0.80	0.90	1.19	0.89	0.33
	12/20	1.0291	1.82	0.75	0.74	1.07	1.01	0.41
	12/25	1.0282	2.75	1.00	1.20	1.75	0.87	0.36
M R	1/18	1.0288	1.63	0.58	0.66	1.05	0.88	0.36
	1/27	1.0286	2.04		0.89			
	1/30	1.0281	2.09	0.85	0.90	1.24	0.94	0.41
	2/5	1.0285	2.30	0.93	0.97	1.37	0.96	0.40
	2/9	1.0293	2.42	0.85	1.00	1.57	0.85	0.35
M H	2/13	1.0269	2.00	0.80	0.88	1.20	0.91	0.40
	2/19	1.0260	1.52	0.65	0.67	0.87	0.97	0.43
	2/25	1.0272	2.54	1.05	1.13	1.49	0.93	0.41

obtained from measurements of specific gravity.¹⁵ The diffusible calcium in the ultrafiltrate was calculated in terms of millimols per kilogram of water, the average room temperature being assumed to be 22.5 C and the presence of other solids being disregarded. Calculations then were made for the concentration of calcium ions from the concentration of serum protein and total calcium according to the relation derived by McLean and Hastings.¹⁶ It will be seen in the table that within the limits of error of the method the ratio of the diffusible calcium to the calculated calcium ions is 0.95 ± 0.02 (standard error). It is of

¹⁵ Sunderman, F. W. Studies on Serum Electrolytes. X. The Water of Serum, *J. Biol. Chem.* **113** 111, 1936.

¹⁶ McLean, F. C., and Hastings, A. B. The State of Calcium in the Fluids of the Body. Conditions Affecting the Ionization of Calcium, *J. Biol. Chem.* **108** 285, 1935.

especial interest to note that the ratio of diffusible calcium to total calcium is fairly constant for each person. There is no evidence to suggest that either the diffusible or the nondiffusible portion of the serum calcium is selectively affected by dihydrotachysterol. This observation is at variance with the conclusions of Holtz, Gissel and Rossmann,⁴ who stated that under the action of dihydrotachysterol the "colloidal" (nondiffusible) fraction was the first to increase and that later an increase occurred in the calcium of the ultrafiltrate. These authors failed to calculate the concentration of serum calcium on a water basis and obtained their figure for "colloidal" calcium by subtracting the value for the diffusible fraction from that for the total calcium. They furnished no data concerning serum protein, total solids

TABLE 7—*Summary of Studies of Calcium Balance*

Subject	Number of Three Day Periods	Therapy	Average Intake for Period, Gm	Average Urinary Calcium for Period, Gm	Average Fecal Cal- cium for Period, Gm	Average Calcium Balance for Period, Gm
J J	2	Vioosterol, calcium	16.50	0.65	15.70	+0.15
	2	None	6.90	0.38	1.43	-0.91
	3	Dihydrotachysterol	0.90	0.44	0.71	-0.25
L H	2	Vioosterol, calcium	17.24	0.97	15.23	+1.04
	2	Vioosterol (only)	2.44	0.19	2.11	-0.14
	2	None	2.70	0.11	2.65	-0.06
	4	Dihydrotachysterol	2.70	0.54	2.77	-0.51
M H	2	Vioosterol, calcium	7.99	0.42	7.76	-0.19
	2	None	3.23	0.23	2.05	+0.94
	2	Dihydrotachysterol	3.33	1.20	1.69	+0.44
H E	2	Vioosterol, calcium	9.26	0.20	8.02	+1.04
	2	None	3.41	0.12	3.38	-0.09
	2	Dihydrotachysterol	3.35	0.75	2.15	+0.45
M R	2	None	2.65	0.65	0.79	+1.21
	6	Dihydrotachysterol	2.71	0.63	0.54	+1.54

or specific gravity from which values for nondiffusible calcium may be recalculated on a water basis. We are unable to confirm their results. Within the limits of error of our method, it appears that there is no evidence of the presence of diffusible nonionized calcium in the serum in significant amounts.

In general, an inverse relation was observed between the concentration of total calcium and that of inorganic phosphorus in the serum. When the concentration of serum calcium returned to normal levels after the administration of effective amounts of dihydrotachysterol, the concentration of inorganic phosphorus also tended to return to the normal range.

In table 7 are summarized the data relating to calcium balance in our patients. It will be seen that the average fecal calcium was less during the periods of dihydrotachysterol therapy than in the control periods without any therapy in 4 of the 5 patients. It will also be seen that urinary excretion of calcium was greater during the periods of dihydrotachysterol therapy than in the control periods without therapy in 4 of

the 5 patients. These data, so far as they permit conclusions, tend to support previous observations that dihydrotachysterol leads to increased urinary excretion of calcium at the expense of fecal calcium.

SUMMARY

Observations are reported on 5 patients with parathyroid deficiency following thyroidectomy who were treated with dihydrotachysterol. These observations included determinations of calcium balance, total and diffusible serum calcium, serum protein and inorganic serum phosphorus before and during the administration of dihydrotachysterol.

Dihydrotachysterol is highly effective in increasing the concentration of serum calcium and in relieving the symptoms of parathyroid deficiency.

In excessive doses it is capable of producing hypercalcemia with toxic symptoms.

The diffusible and the nondiffusible fraction of the serum calcium share about equally in the rise in concentration of total serum calcium which follows the administration of dihydrotachysterol.

Insofar as the data permit conclusions, the trend of changes in the urinary and the fecal calcium in our cases supports previous opinion that dihydrotachysterol increases urinary excretion of calcium at the expense of fecal calcium.

Part of the dihydrotachysterol used was donated by the Winthrop Chemical Co., Inc., New York.

EVALUATION OF SULFANILAMIDE IN THE TREATMENT OF PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS

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MINNAPOLIS

Sulfanilamide (paraaminobenzenesulfonamide) is effective in the treatment of infections due to beta hemolytic streptococci. Clinical and experimental observations indicate that this chemotherapeutic agent may be of value in the treatment of infections caused by the less virulent classes of streptococci. The hemolytic streptococci designated as the alpha group include *Streptococcus viridans*. Bliss, Long and Feinstein¹ observed that the growth of forty-two of forty-five strains of alpha hemolytic streptococci was inhibited by a 1:10,000 concentration of the drug.² Long and Bliss³ found that sulfanilamide exerted a definite bacteriostatic effect in urine cultures of alpha streptococci. It would be desirable to ascertain the effect of sulfanilamide on the lesions of animals infected with the less virulent groups of streptococci, but such infections are not easily produced. Muether and Kinsella⁴ stated that they established bacterial endocarditis with persistent bacteremia in dogs, using a culture of nonhemolytic streptococci. After daily oral administrations of sulfanilamide, 4 of 5 dogs made a complete recovery.

Read in part at a meeting of the Minnesota Society of Internal Medicine, June 4, 1938

From the Department of Medicine, University Hospitals, University of Minnesota Medical School

1 Bliss, F. A., Long, P. H., and Feinstein, W. H. The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy, *South M J* **31** 303 (March) 1938

2 Dr. Perrin Long informed us that these 45 strains of alpha streptococci were isolated from 45 patients with subacute bacterial endocarditis. The 3 strains for which sulfanilamide was not bacteriostatic were *Str. viridans*, but belonged to the enterococcus group, as do about 10 to 15 per cent of the *viridans* strains which are recovered from the blood of patients with subacute bacterial endocarditis.

3 Long, P. H., and Bliss, E. A. Observations upon the Mode of Action and the Clinical Use of Sulfanilamide in Urinary Tract Infections, *South M J* **31** 308 (March) 1938

4 Muether, R. O., and Kinsella, R. A. Sulfanilamide in the Treatment of Experimental Endocarditis, *J A M A* **110** 603 (Feb. 19) 1938

from the infection. In a discussion of these results, Muether expressed the opinion that sulfanilamide is of no value in the treatment of subacute bacterial endocarditis in man.

There are few available data in the literature concerning the results of sulfanilamide therapy in patients with infections due to *Str. viridans*. At the Johns Hopkins Hospital ¹ 2 patients with infections of the soft tissues responded quickly to sulfanilamide, and 2 patients with infections of the urinary tract made prompt recoveries. Love ⁵ has reported a case of meningitis due to a gram-negative nonhemolytic streptococcus which responded favorably to sulfanilamide and prontosil ⁶.

The etiologic agent in subacute bacterial endocarditis is usually *Str. viridans*. There is considerable uncertainty as to whether sulfanilamide is of any value in this disease. Bliss, Long and Femstone ¹ treated 3 patients with massive doses of the drug, with the result that cultures of the blood remained sterile, but the course of the disease was not altered. Klee and Romer ⁷ administered prontosil ⁸ to 5 patients with subacute bacterial endocarditis, with no beneficial results. On the other hand, Hussey ⁹ reported in detail a case of bacterial endocarditis in which the patient was apparently cured by sulfanilamide. The causative organism in his case was a beta hemolytic streptococcus. More recently, Major and Leger ¹⁰ have recorded in detail a case of subacute bacterial endocarditis with *Str. viridans* as the etiologic agent. They stated that recovery followed the use of prontosil, ⁶ but that the patient died of heart failure twenty-nine days after the temperature had become normal and twelve days after prontosil ⁶ had been discontinued. A microscopic section of the aortic valve, obtained at autopsy, showed clumps of gram-positive diplococci deep beneath the healed surface. Cultures of material from excised portions of the mitral and aortic valves were sterile.

5 Love, J. W. Nonhemolytic Streptococcus Meningitis. Report of a Case Successfully Treated with Sulfanilamide and Prontosil, *J. Lab. & Clin. Med.* **23** 482 (Feb.) 1938.

6 The preparation used was disodium 4-sulfamidophenyl-2'-azo-7'-acetylaminio-1'-hydroxynaphthalene-3',6'-disulfonate. This is now known as neoprontosil.

7 Klee, P., and Romer, H. Prontosil bei Streptokokkenerkrankungen, *Deutsche med. Wchnschr.* **61** 235 (Feb. 15) 1935.

8 The formula is not given in the report. The preparation used was probably the original prontosil (4-sulfamido-2',4'-diaminoazobenzene hydrochloride), a compound that has been little used in this country.

9 Hussey, H. H. Probable Bacterial Endocarditis Apparently Cured with Sulfanilamide. Report of a Case, *M. Ann. District of Columbia* **6** 275 (Sept.) 1937.

10 Major, R. H., and Leger, L. H. Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, *J. A. M. A.* **111** 1919 (Nov. 19) 1938.

Our interest in treating several patients with subacute bacterial endocarditis with sulfanilamide was the result of a sequence of events observed in 2 patients (cases 1 and 2) which followed administration of the drug, and of the paucity of detailed clinical studies available in the literature. In initiating this study, we were fully aware of the nature of the endocardial lesion in this disease. Before the introduction of sulfanilamide, Swift¹¹ stated the problem of therapy for subacute bacterial endocarditis as follows:

When one recognizes that the vegetations are thick masses of material in which the bacteria are actively growing, and that many of the bacterial agglomerations are situated at a considerable distance from any circulating blood, it is difficult to understand how any therapeutic agent introduced into the blood stream can have a completely effective bactericidal action throughout the entire extent of the vegetation.

We also recognized that there is an accumulating body of evidence¹² that patients with subacute bacterial endocarditis may occasionally recover from the disease. In the event of such an outcome in a well established case there might be a considerable temptation to ascribe the result to the use of certain therapeutic agents.

METHOD OF STUDY

During the past year 12 patients with subacute bacterial endocarditis have been treated with sulfanilamide. While a correct diagnosis of this disease is attended with difficulty, we relied principally on (1) the history, (2) the presence of an organic cardiac murmur, which changed in intensity from time to time, (3) the manifestations of embolic phenomena, and (4) the demonstration of persistent bacteremia. Though instances of subacute bacterial endocarditis without bacteremia do occur,¹³ we recovered organisms repeatedly from the blood of all 12 patients. The patients included 10 females and 2 males. Their ages varied between 18 and 70 years. Six patients, all females, had a congenital cardiac lesion. Three had a patent ductus arteriosus, 2 had a patent interventricular septum, and 1 had coarctation of the aorta with a bicuspid aortic valve. There were 4 patients with rheumatic heart disease. Three had mitral stenosis, and a fourth had an aortic lesion in addition to

11 Swift, H. F. Subacute Bacterial Endocarditis, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937, vol. 4, p. 323.

12 Libman, E. A Further Report of Recovery and Recurrence in Subacute Bacterial Endocarditis, *Tr. A. Am. Physicians* **48**: 44, 1933. Weiss, S., and Rhoads, C. P. Healing and Healed Vegetative (Subacute Bacterial) Endocarditis, *New England J. Med.* **199**: 70 (July 12) 1928. Hamman, L. Healed Bacterial Endocarditis, *Ann. Int. Med.* **11**: 175 (July) 1937.

13 Keefer, C. S. Subacute Bacterial Endocarditis—Active Cases Without Bacteremia, *Ann. Int. Med.* **11**: 714 (Nov.) 1937.

mitral stenosis One elderly patient had aortic stenosis thought to be due to arteriosclerosis, but while he was under observation a persistent diastolic murmur became audible over the aortic area One patient had bacterial vegetations on an otherwise normal cardiac valve, the condition being demonstrated at autopsy The etiologic agent was *Str viridans* in 11 cases and *Staphylococcus albus* in 1 All eleven strains of *Str viridans* showed the typical green type of hemolysis when streaked out on blood agar plates and when studied by the pour plate technic Veal infusion agar with a p_H of 7.4 to 7.6 was used throughout this study Sulfanilamide was given orally, whenever possible, in daily divided doses totaling between 45 and 100 grains (2.91 and 6.48 Gm) As a precautionary measure against the development of acidosis, 5 to 15 grains (0.32 to 0.97 Gm) of sodium bicarbonate was given orally with each dose of sulfanilamide

REPORT OF CASES

CASE 1—E. L., a 35 year old white woman, was admitted to the hospital on March 27, 1937 She was in good health until seven months before entry, when she noticed unusual fatigue, weakness, fever and chills Her appetite was poor, and she noted a progressive loss of weight The symptoms continued unabated until admission to the hospital There was no history of rheumatic fever or of chorea, and she had no knowledge of an organic cardiac lesion prior to her present illness

Physical examination showed that the patient was emaciated and poorly developed and appeared chronically ill The skin of the face and arms exhibited a diffuse brownish pigmentation There were no petechiae on the mucous membranes of the eyes or mouth The lungs were normal The blood pressure was 88 mm of mercury systolic and 56 mm diastolic On percussion the heart was found to be enlarged to the left The apical impulse was prominent A diastolic thrill was palpable at the apex On auscultation over the apex an early systolic thrill following the first sound was detected The second sound was obscured by a high-pitched diastolic murmur The pulmonic second sound was accentuated The cardiac rhythm was regular The spleen was firm and slightly tender and was palpable 3 cm below the costal margin The liver was not felt No peripheral edema was present

Laboratory examination showed that the value for hemoglobin was 57 per cent (16.5 Gm per hundred cubic centimeters, equivalent to 100 per cent [Sahli¹⁴]), for erythrocytes 2,600,000 per cubic millimeter and for leukocytes 4,900 per cubic millimeter Examination of the urine revealed numerous leukocytes in the sediment Serologic tests of the blood for syphilis gave negative results A culture of the blood taken on each of four successive days yielded *Staph albus*, with 4 to 11 colonies per cubic centimeter of blood

The patient was given 4 Gm of sulfanilamide a day by mouth Within a few days there was a marked decrease in her temperature (fig 1), and she felt considerably improved It is of interest, in the light of subsequent findings, that a teleroentgenogram taken at this time showed a heart shadow with both right and left ventricular enlargement The esophagus was slightly displaced posteriorly in the region of the left atrium

14 This value was used throughout our studies

On the seventeenth day after admission the patient's condition became suddenly worse. She was drowsy and responded only to painful stimuli. The pupils were dilated, and definite rigidity of the neck was noted. The reflexes were hypoactive but equal. A lumbar puncture showed the pressure of the spinal fluid to be 24 mm of mercury. The fluid was cloudy and contained 350 cells per cubic millimeter, 75 per cent of which were polymorphonuclear neutrophils and 25 per cent lymphocytes. The value for total protein was 151.6 mg per hundred cubic centimeters. Smears and cultures of the fluid showed *Staph. albus* on several occasions. The blood culture at this time yielded the same organism. For seven days the patient was given a total of 4 Gm of sulfanilamide a day. This was

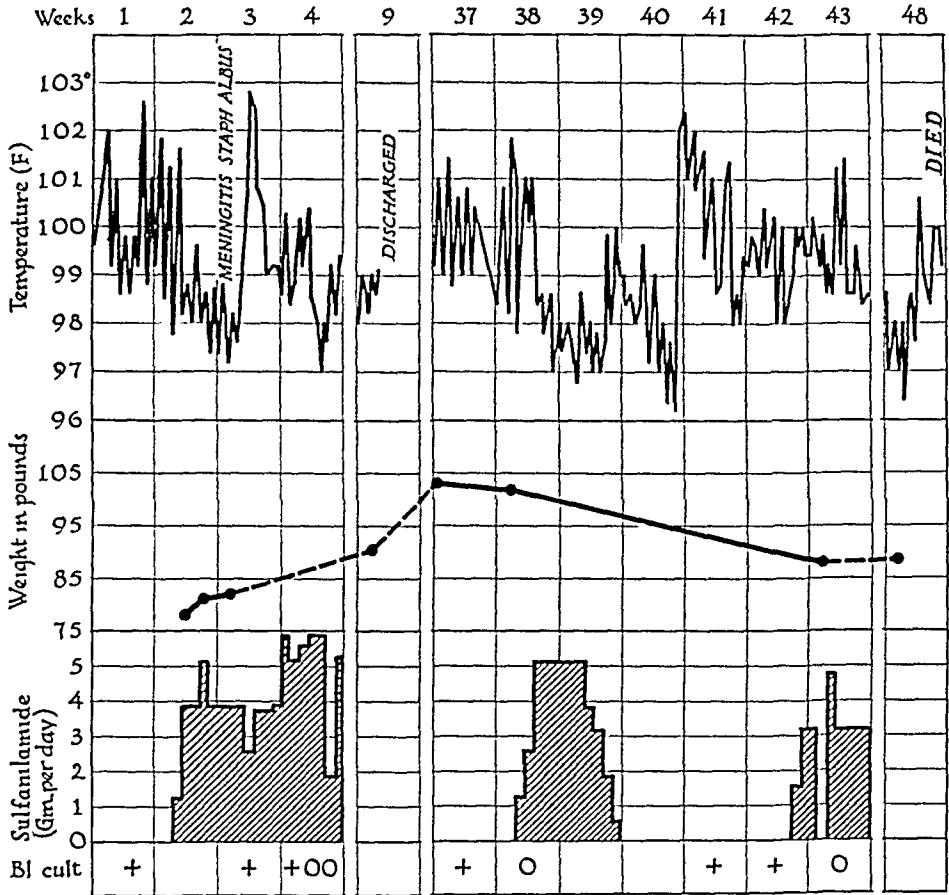


Chart 1—Subacute bacterial endocarditis and meningitis due to *Staph. albus* (case 1). After the administration of sulfanilamide the patient became afebrile and gained weight, and the blood cultures were sterile.

administered subcutaneously and intrathecally. Her condition improved rapidly. By the twenty-sixth day of hospitalization her temperature was normal. In the meantime, cultures of the blood and spinal fluid were sterile. The patient's weight on admission to the hospital was 80 pounds (36.3 Kg), and when she was discharged, on June 24, she weighed 91 pounds (41.3 Kg). The cardiac findings remained essentially the same.

She returned home and was able to assume her household activities. In August 1937 her weight was 120 pounds (54.4 Kg), representing a gain of 40

pounds (181 Kg) She was instructed to take her temperature three times a day, and at no time did she have fever, until December 15, when she contracted an infection of the upper respiratory tract Because the fever persisted, she was advised to enter the hospital on Jan 4, 1938 There was an increase in cardiac dulness as compared with the finding in the previous examination A systolic and a diastolic thrill were present over the apex Harsh systolic and diastolic murmurs were heard over the same area On auscultation the lungs were found to be clear The liver was just palpable, and the spleen was felt 2 cm below the costal border There was no peripheral edema The value for hemoglobin was 70 per cent The blood count showed 3,400,000 erythrocytes and 8,700 leukocytes per cubic millimeter The urine contained a trace of albumin, and there were many leukocytes in the sediment Staph albus was persistently present in several blood cultures A teleroentgenogram and an esophogram showed a definite displacement of the esophagus to the right and posteriorly in the region of the left auricle

During the first nine days after admission she was febrile in the afternoon On the tenth day sulfanilamide therapy was again instituted After this her temperature returned to normal and blood cultures were sterile After sulfanilamide had been given for one week, marked anorexia developed The drug was then given subcutaneously as an 0.8 per cent solution in physiologic solution of sodium chloride, but the anorexia continued, with nausea and vomiting Sulfanilamide therapy was then discontinued The patient continued to have anorexia, though the nausea and vomiting abated On the twenty-sixth day of hospitalization signs of cardiac failure appeared for the first time There was edema of the face and extremities There was evidence of pulmonary congestion The liver was now palpable 6 cm below the costal margin and was tender After the use of diuretics the signs of congestive heart failure diminished The temperature became elevated, and Staph albus was isolated from the blood cultures Sulfanilamide was given subcutaneously, and again the temperature became normal and the blood cultures sterile The nausea and vomiting returned, however, and no further attempts were made to give sulfanilamide The signs of cardiac decompensation returned and became progressively more marked The patient died on March 25

Autopsy was done by Dr Robert Hebbel The heart weighed 360 Gm The epicardium and myocardium appeared normal The valvular abnormalities were limited to the mitral valve There were multiple small, reddish, friable vegetations on its auricular surface, most of which were at some distance from the free margin The vegetations were more numerous above the posterior than above the anterior leaflets There were a few scattered vegetations through the wall of the left auricle A few vegetations were observed on the ventricular surface of the anterior mitral leaflets, near the line of closure Staph albus was cultured from the vegetations The leaflets were not thickened There was slight atherosclerosis of the coronary vessels

The spinal cord was exposed and appeared normal A stained section of the thoracic portion of the spinal cord, examined microscopically, showed no abnormality

The pathologic diagnosis was subacute bacterial endocarditis, congestive heart failure, infarcts of the lungs and kidneys, thrombosis of the right pulmonary artery, bronchopneumonia, and subacute splenitis

The clinical course of the second patient (case 2) merits a detailed description because when first seen she presented a definite clinical picture of severe subacute bacterial endocarditis She has been free of

any evidence of infection for nine months after her discharge from the hospital

CASE 2—B G, an 18 year old white girl, single, entered the hospital on Sept 27, 1937 All her life she had had dyspnea on exertion She had never been cyanotic Seven months before admission she became increasingly weak and observed pallor of her features Five months later she had a sudden onset of pain in the right lower quadrant of the abdomen and the left side of the chest Her temperature was 103 F She had a cough productive of blood-tinged sputum These symptoms subsided in a week, but left her feeling tired and listless Prior to admission, she had been confined to bed for three weeks At this time she noted "blood blisters" over the skin of the lower extremities These ruptured and became crusted Two weeks before admission she had several tarry stools She felt drowsy and had severe headaches Edema of the ankles was observed She had lost 20 pounds (9.1 Kg) in weight over a period of four months The menses had been regular until one year before her present illness, but since then had been scanty and irregular She had never had rheumatic fever, chorea or scarlet fever

Physical examination revealed an apathetic, undernourished girl with a peculiar yellowish pallor There was no icterus of the scleras Cyanosis was not present There were no petechiae of the mucous membranes of the scleras and mouth The lungs were normal The heart did not appear enlarged on percussion The blood pressure was 112 mm of mercury systolic and 60 mm diastolic The heart sounds were distant and regular There was a systolic murmur over the pulmonic area which radiated to the left clavicle, and at times a faint diastolic murmur was heard in the same region A blowing systolic murmur was heard at the apex The liver was palpated 5 cm below the costal margin and was tender and soft The spleen was tender and soft and was felt 2 cm below the costal margin There was edema of the lower parts of the legs Numerous small reddish brown pigmented areas were present in the skin of the lower extremities, which were the sites of the previously mentioned "blood blisters"

Examination of the urine showed albuminuria on two occasions, and there were numerous erythrocytes in the sediment The value for hemoglobin on admission was 30 per cent, there were 1,600,000 erythrocytes per cubic millimeter The leukocytes numbered 6,200 per cubic millimeter Occasional reticuloendothelial cells were seen in stained blood films The value for the total plasma proteins was 6.7 Gm per hundred cubic centimeters The sedimentation rate was 97 mm in one hour (Westergren) Str. viridans was obtained several times from cultures of the blood Colony counts showed 30 colonies per cubic centimeter on one occasion and 200 colonies on another The stools did not contain occult blood

A teleroentgenogram taken shortly after entry was interpreted as showing questionable enlargement of the left ventricle and an area of either consolidation or infarction of the lower left pulmonary field However, later fluoroscopic examination showed definite prominence of the cardiac shadow in the region of the pulmonary conus These observations, in addition to the physical examination, led us to believe that the patient had a patent ductus arteriosus with bacterial vegetations at that site

She was given a transfusion of 500 cc of citrated blood Because of the severity of her illness and because sulfanilamide had appeared to have a temporary beneficial effect on the patient in case 1 she was given the drug by mouth (fig 2) Coincident with the administration of sulfanilamide there was a decline in the temperature, and the blood cultures remained sterile, with one exception

The patient exhibited no untoward reactions to the drug. The hematuria, which was present for several days after admission, gradually subsided, with no reduction in renal function. Five weeks after entry, two additional transfusions were necessary because of a fall in the erythrocyte level. Three months after entry the value for hemoglobin was 82 per cent and the erythrocyte count 5,300,000 per cubic millimeter. The leukocyte count remained normal or slightly elevated throughout the course. An intradermal test made with a nucleoprotein fraction of hemolytic streptococcus gave a negative reaction on admission, but five weeks later, when the test was repeated, the result was strongly positive. There was

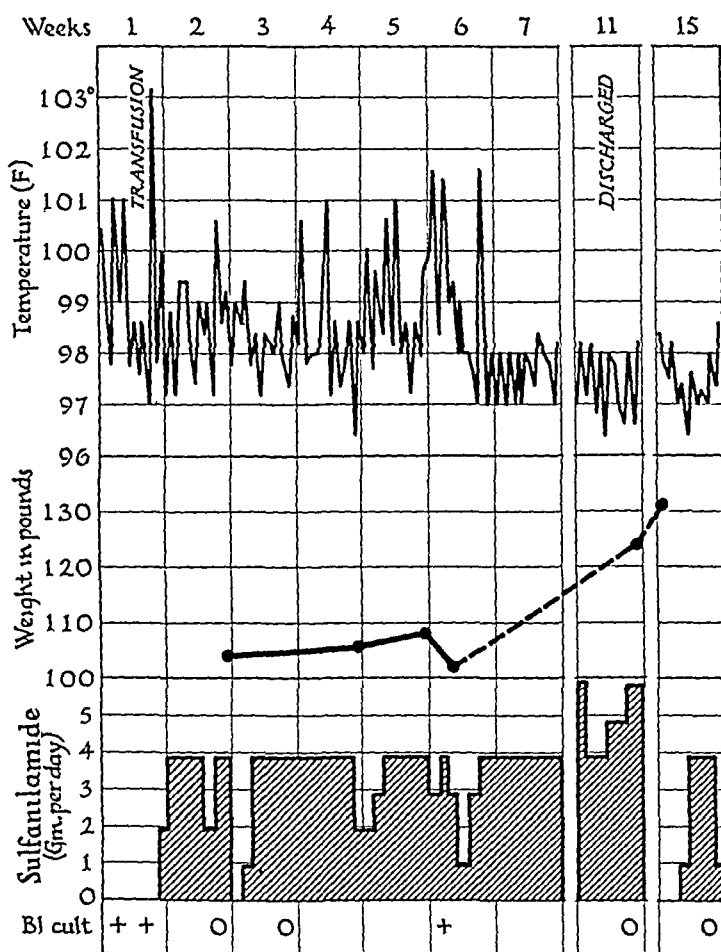


Chart 2—Subacute bacterial endocarditis due to *Str. viridans*. The patient became afebrile and gained weight, and the blood cultures remained sterile. The patient remained well nine months after sulfanilamide therapy.

gradual improvement in the patient's general condition. The liver and spleen were no longer palpable. The systolic and diastolic murmurs over the pulmonic area became more prominent, but no change was demonstrable in the size of the heart. The patient's weight two weeks after entry was 104 pounds (47.2 Kg), and when she was discharged from the hospital, on December 14, her weight was 124 pounds (56.2 Kg).

She was seen again nine months after leaving the hospital. She weighed 130 pounds (59 Kg). Her only complaint was dyspnea on exertion. She was working daily in a truck garden. On examination the systolic and diastolic murmurs were found to be slightly more pronounced over the pulmonic area. The pulmonary

conus still showed enlargement when examined fluoroscopically. The spleen was palpable 2 fingerbreadths below the costal margin. She had not taken sulfanilamide during the intervening time.

The observations made in the preceding 2 cases lead one to assume an optimistic outlook concerning the value of sulfanilamide in the therapy of subacute bacterial endocarditis. We were fortunate in being able to study 10 additional patients and to observe less favorable results.

The following case is that of a patient with a congenital cardiac lesion, probably a patent interventricular septal defect with superimposed bacterial vegetations. Although she had a relatively mild clinical course, prolonged administration of sulfanilamide failed to sterilize the blood stream and did not appear to benefit her. Dr. Ruth Boynton, director of the University of Minnesota Health Service, and her associates gave us the opportunity of observing this patient.

CASE 3—L. J., a 20 year old woman, single, entered the University of Minnesota Health Service on Feb. 14, 1938, complaining of weakness and fatigue. She had had dyspnea on exertion since early childhood. When she first entered grade school she was told that she had a cardiac murmur. On Jan. 6, 1938, she first noted lack of appetite and felt very tired. These symptoms were followed by headaches, generalized weakness and a slight fever. Rest in bed did not alleviate her symptoms, and she was advised to enter the hospital.

Physical examination showed her to be well developed and well nourished but apathetic and listless. Results of further examination were within normal limits except for a harsh systolic murmur at the apex. She presented a difficult problem in diagnosis. Pelvic and neurologic examination gave normal results. The spinal fluid showed no abnormality. The value for hemoglobin was 74 per cent. There were 4,470,000 erythrocytes and 12,900 leukocytes per cubic millimeter of blood. Culture of the blood on admission to the hospital showed no growth. The daily temperature ranged between 98.6 and 101.5 F. Approximately three weeks after admission she complained of pain at the base of the right great toe, and at this time small hemorrhagic areas appeared in the overlying skin on the plantar surface. Shortly thereafter the blood cultures contained *Streptococcus viridans*, with 1 to 14 colonies per cubic centimeter of blood. A cutaneous test with the nucleoprotein of *Streptococcus haemolyticus* gave a negative result.

Since the illness appeared to be of short duration and the patient did not seem to be in serious condition, it was felt that sulfanilamide should be administered. She was given a total of 276 Gm. of the drug by mouth over a period of sixty-seven days. The daily dose varied between 60 and 75 grams. The cardiac murmur increased in intensity. There was no improvement in the clinical condition. There was continued evidence of bacteremia, although the cultures were occasionally sterile. The drug appeared to make the patient more lethargic and listless. In spite of anorexia she maintained her nutritional status. She had only moderate hypochromic anemia. No toxic manifestations were noted except for increased lethargy. It was apparent that sulfanilamide had been of no value to this patient, and she was sent home on May 17.

We had the opportunity in the following case of administering two different chemical compounds, to ascertain their effects. The patient was

first given sulfanilamide (paraaminobenzenesulfonamide) and then 4 (4'-aminobenzenesulfonamide) benzenesulfondimethylamide

CASE 4—N N, a 25 year old white, single woman, entered the hospital on Sept 10, 1937. She had been in good health up to four months previously, when she had a sore throat and severe occipital headaches. The sore throat persisted for three weeks and was accompanied by fever and progressive weakness. On three or four occasions she observed small red spots on her arms, which remained a few days and then disappeared. She had a cough productive of blood-streaked sputum and at one time had pain in the right lower part of the chest. She had never been known to have a cardiac lesion before her present illness. She had never had rheumatic fever or chorea.

On physical examination she appeared fairly well developed, but poorly nourished. There was marked pallor of the features and mucous membranes. The heart was found to be slightly enlarged on percussion. A systolic thrill was felt at the apex and another thrill just to the left of the sternum, in the third interspace. A loud, blowing systolic murmur was heard over the apex, which obscured the heart sounds and was transmitted to the axilla. A loud, rough systolic murmur was present in the third interspace, just to the left of the sternal border. The second pulmonic sound was accentuated. The rhythm was regular, and the blood pressure was 96 mm of mercury systolic and 70 mm diastolic. The lungs were within normal limits. The spleen and liver were not palpable. There was no edema of the lower parts of the legs.

The value for hemoglobin on entry was 57 per cent. There were 3,200,000 erythrocytes and 9,800 leukocytes per cubic millimeter of blood. Streptococci of the viridans type were cultured from the blood, and a pour plate showed 10 colonies per cubic centimeter of blood.

Fluoroscopic examination of the heart showed slight enlargement of the right and left ventricles, without any other demonstrable enlargement. There was no displacement posteriorly of the esophagus as observed after filling with barium sulfate.

A diagnosis of congenital heart disease with a patent interventricular septum was made. Because of her poor condition the patient was given three transfusions of blood during the first week of observation. This was followed by some improvement. During the third week she was given 45 to 60 grains (2.91 to 3.88 Gm) of sulfanilamide a day. There was no appreciable change in her clinical condition during administration of the drug, although the blood cultures were sterile. She was then given 4 (4'-aminobenzenesulfonamide) benzenesulfondimethylamide in smaller doses. Although her temperature approached normal, streptococci were isolated from the blood. She became extremely ill, with signs of congestive heart failure and jaundice. The medication was discontinued. She was given a transfusion of blood, but her condition became progressively worse, and she died on November 7. Autopsy was not performed.

The patient in the following case had marked bacteremia and an unusual type of cardiovascular lesion. After the oral administration of sulfanilamide the blood stream was sterilized and she became afebrile. Nevertheless, her illness terminated fatally. The case is reported in more detail elsewhere¹⁵

15 Hallock, P., and Hebbel, R. Coarctation of the Aorta, Nonclinical Type, Associated with Congenitally Bicuspid Aortic Valve. A Method for Its Recognition, *Am Heart J* **17** 444 (April) 1939.

CASE 5—E W, a 31 year old white woman, married, first entered the hospital on Aug 14, 1937, complaining of pain in the left flank and intermittent chills and fever of about five months' duration. Physical examination showed that she was poorly developed and appeared chronically ill. There was a systolic pulsation in the suprasternal notch, with a systolic thrill. The heart did not appear enlarged on percussion. A soft midsystolic murmur was heard at the apex. Over the aortic area there was a low-pitched systolic murmur, followed first by an accentuated aortic second sound and then by a high-pitched, short diastolic murmur. The blood pressure was 104 mm of mercury systolic and 70 mm diastolic. Tenderness was elicited in the left flank on deep palpation, but no mass was felt. Fluoroscopic examination of the heart and great vessels by Dr Philip Hallock showed dilatation of the aorta in the region of the common carotid and subclavian arteries, with a constriction between this dilatation and the ascending aorta.

It was thought that the patient had coarctation of the aorta and a congenital bicuspid aortic valve. She was febrile while under observation. On September 2 before further studies could be undertaken, she left the hospital, against advice.

She reentered the hospital on November 7. There had been no remarkable change in her condition until one week before, when she suffered from a sudden and sharp pain over the precordium, which radiated to the left shoulder and down the left arm. Such attacks, which were transient, occurred several times. She had had severe chills and a temperature of 104 F. At the time of admission she had petechiae of both conjunctivas and of the skin over the abdomen and chest. She complained of pain in the tips of her fingers. A harsh diastolic murmur was now heard over the aortic area and was transmitted down the left border of the sternum. The blood pressure was 130 mm of mercury systolic and 60 mm diastolic. The pressure was essentially the same in all four extremities. The margin of the liver was tender and was palpated 3 cm below the right costal margin. The spleen was not felt.

The urine contained albumin, with leukocytes and erythrocytes in the sediment. The value for hemoglobin was 58 per cent. The erythrocyte count was 2,600,000 and the leukocyte count 6,000 per cubic millimeter. A blood culture on entry showed *St. viridans*, with 100 colonies per cubic centimeter of blood.

The patient was given 90 grains (5.82 Gm) of sulfanilamide a day for eleven days. The free sulfanilamide in the blood varied between 7 and 86 mg per hundred cubic centimeters. Under this regimen the temperature approached normal and the blood cultures were sterile, but the patient's condition grew progressively worse. She died on November 27.

An autopsy, done by Dr Robert Hebbel, disclosed a bicuspid aortic valve with soft, friable vegetations on the margins and scattered vegetations on the ventricular margins below the right cusp. Coarctation of the aorta was present. There were multiple infarcts of the kidneys and spleen.

Four patients were studied who had rheumatic heart disease with superimposed bacterial endocarditis. The patient in the following case was given small doses of sulfanilamide in order that the effect on the bacteremia and on the clinical course might be observed.

CASE 6—A S, a 23 year old white woman, married, entered the hospital on Nov 4, 1937. Eleven years previously she had had acute rheumatic fever with resultant mitral valvulitis. Three years later she had congestive heart failure, followed by another attack of rheumatic fever. Four months before her present admission she noticed anorexia, weakness and dizziness. She became dyspneic

on exertion. Two months before admission she had chills and a temperature of 103 F. Profuse nocturnal sweats were present for two months. There was a recent loss of 25 pounds (11.3 Kg) in weight.

On examination she appeared fatigued and chronically ill and showed evidence of recent loss of weight. There was marked pallor of the features and mucous membranes. Petechiae were present in the skin of the abdomen. The veins of the neck were distended. On percussion the heart was found to be enlarged, particularly in the region of the pulmonary cone. A systolic thrill was felt over the precordial area, with a loud, harsh systolic murmur on auscultation. No diastolic murmur was heard. The blood pressure was 110 mm of mercury systolic and 70 mm diastolic. The edge of the liver was felt 3 cm below the costal margin, and the spleen was tender and easily palpable.

Laboratory data included the finding of erythrocytes and leukocytes in the sediment of the urine. The value for hemoglobin was 67 per cent, there were 3,500,000 erythrocytes and 19,400 leukocytes per cubic millimeter of blood. Cultures of the urine and blood yielded *Str. viridans*. There were 2 colonies per cubic centimeter of blood.

During her entire stay in the hospital the patient suffered from excruciating pain due to emboli. Her temperature ranged between 98.6 and 104 F. She perspired profusely. Sulfanilamide was given orally in doses of 40 grains (2.59 Gm) daily for eleven days. The free sulfanilamide content of the blood varied between 3.3 and 4 mg per hundred cubic centimeters. In addition, she was given two blood transfusions. Her condition became progressively worse. We wished to continue the administration of sulfanilamide in larger doses, but on December 18 she left the hospital against advice. She died at home three months later. Autopsy was not performed.

The patient in the following case had a severe form of rheumatic valvulitis involving the mitral and aortic valves. Coincident with the administration of sulfanilamide he became afebrile and felt greatly improved, but the blood cultures continued to show *Str. viridans* in large numbers.

CASE 7—R. S., a 36 year old white man, single, entered the hospital on Sept. 14, 1937. The patient had had his first attack of rheumatic fever nine years before entry, and since that time he had had recurrent attacks. He was known to have rheumatic involvement of both the aortic and the mitral valve. Five months before his present admission he had polyarthritides with chills and fever, which persisted until entry. He had progressive weakness, anorexia, nausea and vomiting.

On examination he appeared ill and poorly nourished. He had pallor and a suggestive icterus of the scleras. Petechiae were present in the conjunctivas. On percussion the heart was found to be enlarged to the left, with marked prominence of the cone. Systolic and diastolic murmurs were present over the apex. There was a diastolic murmur over the aortic area, which was transmitted down the left border of the sternum. The blood pressure was 124 mm of mercury systolic and 50 mm diastolic. The liver and spleen were not palpated.

The urine showed persistent albuminuria, with red blood cells, leukocytes and granular casts in the sediment. The value for hemoglobin was 56 per cent, there were 3,300,000 erythrocytes and 9,200 leukocytes per cubic millimeter of blood. A blood culture showed 65 colonies of *Str. viridans* per cubic centimeter.

The patient's temperature varied between 98.6 and 102 F before the administration of sulfanilamide. He was given 60 grains (3.88 Gm) of sulfanilamide daily for twenty-three days. Two blood transfusions were also given. After receiving the drug he became afebrile for nine days prior to leaving the hospital. He felt considerably improved. However, the organisms in cultures of the blood remained, quantitative studies showing 200 per cubic centimeter of blood. He was instructed to take the drug at home in doses of 60 grains (3.88 Gm). After his discharge from the hospital, on October 14, his condition became worse, and he died at home three months later. Autopsy was not performed.

The patient in the following case had rheumatic heart disease with involvement of the mitral valve. Although the level of free sulfanilamide in the blood was 13 mg per hundred cubic centimeters for several days, the bacteremia persisted, and the course terminated fatally.

CASE 8—L. R., a 29 year old white woman, married, entered the hospital on July 13, 1938. She had scarlet fever at the age of 6 years, which was followed by "leakage of the heart." She had led a normal life and had four pregnancies, without any complications. Eight months before entry she had weakness, followed by many attacks of pleuritis. Five months later she had a persistent cough, severe anemia, swelling of the ankles and red spots on her arms and legs. Six weeks before entry she had hematuria, chills and fever.

On examination she appeared chronically ill. The mucous membranes were pale. Percussion showed that the heart was enlarged in the second and third left interspaces. A loud systolic murmur was heard over the entire precordium and was transmitted to the axilla and the back. There was no systolic murmur. The blood pressure was 168 mm of mercury systolic and 65 mm diastolic. Rales were heard at the bases of both lungs. The liver was palpable. The spleen was not felt.

Specimens of urine showed persistent albuminuria, with erythrocytes, leukocytes and cellular and granular casts in the sediment. The value for hemoglobin was 45 per cent, there were 3,800,000 erythrocytes and 15,000 leukocytes per cubic millimeter of blood. Cultures of the blood showed *Str. viridans*, with 360 colonies per cubic centimeter of blood.

The patient was given 60 grains (3.88 Gm) of sulfanilamide orally each day for thirty-four days. She also received seventeen transfusions. The level of free sulfanilamide in the blood remained at 13 mg per hundred cubic centimeters for several days. She continued to have bacteremia. Her temperature remained elevated. Her condition became progressively worse, and she died on August 27.

Autopsy—The heart weighed 445 Gm. The leaflets of the mitral valve were destroyed by large fungating and ulcerating vegetations. A few vegetations were present on the aortic valve. There were infarcts of the spleen and left kidney. The kidneys showed acute proliferative glomerulonephritis.

The fourth patient with rheumatic heart disease and subacute bacterial endocarditis also received large amounts of sulfanilamide. The level of free sulfanilamide in the blood reached 18.3 mg per hundred cubic centimeters, without any beneficial effect on the clinical course.

CASE 9—W. B., a 66 year old white man, entered the hospital on July 21, 1938. Three months before entry he had a gastrointestinal disturbance and vomited

several times After this he became weak and dyspneic and lost considerable weight He had no chills or fever There was no history of rheumatic fever, chorea or scarlet fever. His wife and one daughter had died of pulmonary tuberculosis

The patient was emaciated and had rhythmic tremors of the arms and facial muscles There were no petechiae of the skin or mucous membranes On percussion the heart did not appear enlarged There was a systolic murmur at the apex, which was transmitted to the axilla The blood pressure was 112 mm of mercury systolic and 62 mm diastolic The lungs were essentially normal The spleen and liver were not palpable

The urine persistently contained albumin, and leukocytes and erythrocytes were present in the sediment The value for hemoglobin was 54 per cent, the erythrocyte count was 2,910,000 per cubic millimeter, and the leukocyte count was normal throughout the period of observation

The diagnosis was doubtful until a culture of the blood showed *Str viridans*, with 150 colonies per cubic centimeter Roentgenologic examination of the patient's chest revealed enlargement of the left ventricle, with fulness in the region of the pulmonary conus

The patient was given from 60 to 100 grains (3.88 to 6.48 Gm) of sulfanilamide daily In addition, he received five transfusions The level of free sulfanilamide in the blood varied between 10 and 183 mg per hundred cubic centimeters The bacteremia persisted, and he continued to have a high fever He showed no improvement The cardiac murmur became louder, petechiae appeared in the mucous membrane of the eyes He died on August 26

Autopsy—The heart weighed 375 Gm There were large ulcerating lesions on the leaflets of the mitral valve Smaller vegetations were seen on the leaflets of the aortic valve The right lung had infarcts, and active tuberculosis was present in the apex of the left lung

The following case is of considerable interest in that the patient was an elderly man with endocarditis involving the aortic valve He had the signs and symptoms of subacute bacterial endocarditis Sulfanilamide was administered, and severe anemia resulted Although his blood became free of bacteria, there was no apparent change in the clinical course

CASE 10—J M, a 70 year old white man, entered the hospital on Feb 4, 1938 He had been examined two years previously in the hospital because of gastrointestinal symptoms At that time no significant cardiac lesion was noted Five months before his present admission he had dysuria, frequency, nocturia, anorexia and loss of weight Three months later he had pain in the lower part of the back, fever, diarrhea and transient paralysis of the right side of the body

Examination revealed the patient to be emaciated and dehydrated, with marked pallor On percussion the heart appeared slightly enlarged to the left The rhythm was regular A systolic murmur was heard over the entire precordium A faint diastolic murmur was heard over the third left interspace, close to the sternum Marked peripheral arteriosclerosis was present The blood pressure was 130 mm of mercury systolic and 64 mm diastolic The edge of the liver was palpated 4 cm below the costal margin The spleen was not felt The prostate was slightly enlarged

The urine contained albumin, casts, red blood cells and leukocytes in the sediment. The value for hemoglobin was 65 per cent. The erythrocyte count was 3,100,000, and the leukocyte count, 12,700 per hundred cubic centimeters of blood. Cultures of the blood showed *Str. viridans*, with 200 colonies per cubic centimeter.

During the period of observation the patient's temperature ranged between 97 and 104 F. He was given 75 grains (4.88 Gm.) of sulfanilamide per day for one week, during this time cultures of the blood were sterile, but the temperature remained elevated and his general condition became worse. The diastolic murmur became more pronounced. The value for free sulfanilamide in the blood was 6 mg. per hundred cubic centimeters. At the end of one week of sulfanilamide therapy the value for hemoglobin was 36 per cent and the red blood cell count 1,950,000 per cubic millimeter. There was no icterus. The drug was discontinued. The patient's condition appeared hopeless. Arrangements for transfusions were undertaken, but his family took the patient home, against advice. He died one week later. Autopsy was not performed.

The last 2 patients included in this series had congenital heart disease with a patent ductus arteriosus. It is of interest to compare the results of sulfanilamide therapy in these cases with the results in case 2, as the same type of lesion was present. Sulfanilamide was administered to both patients over a long period without any appreciable beneficial effects.

CASE 11—L. M., a 40 year old white, single woman, entered the hospital on March 25, 1938. At 14 years of age she was told that she had "leakage of the heart." For years she had had dyspnea on exertion. Four months before entry she noticed progressive weakness. One month later a physician observed that she had fever and stated that she had pulmonary tuberculosis. Two months before entry she suffered from chills, fever and loss of weight. Another physician advised care at a sanatorium for tuberculosis. She entered a sanatorium, where she was observed for one month, but there was no evidence of pulmonary tuberculosis. She was then transferred to the University Hospitals.

Examination showed the patient to be poorly developed and poorly nourished. Petechiae were present in the mucous membranes of both eyes. Crepitant rales were heard over the lower lobe of the left lung posteriorly. The heart was found to be enlarged on percussion, particularly in the region of the pulmonary conus. A systolic thrill was felt over the region of the conus, and on auscultation a "machinery-like murmur" was heard. The pulmonic second sound was loud and snapping. The blood pressure was 130 mm. of mercury systolic and 68 mm. diastolic. The liver and spleen were not palpable. There was no peripheral edema.

Fluoroscopic examination of the heart and great vessels showed enlargement of the pulmonary artery and the right ventricle. A roentgenogram was interpreted as showing an infarct of the left lung.

The value for hemoglobin was 62 per cent. There were 3,400,000 erythrocytes and 22,000 leukocytes per cubic millimeter of blood. The initial blood culture contained *Str. viridans*, with over 100 colonies per cubic centimeter.

The patient was under observation in the hospital for eighty-three days. She was given a total of 4,140 grains (268.2 Gm.) of sulfanilamide in fifty-eight days. The average daily dose was about 70 grains (4.53 Gm.). The free sulfanilamide in the blood averaged 6.6 mg. per hundred cubic centimeters. The

highest level was 10.4 mg per hundred cubic centimeters, observed while she was receiving 100 grains (6.48 Gm) a day. Shortly after sulfanilamide was given, the blood cultures were sterile. When the drug was discontinued on two occasions for short periods, *Str. viridans* was isolated from the blood. The drug had no apparent effect on the temperature, as the patient was febrile throughout the period of observation. She was listless and had marked anorexia, which was apparently due to sulfanilamide. She lost 20 pounds (9.1 Kg) in weight. It was apparent that the drug had only a temporary effect on the bacteremia, since she desired to go home, she left the hospital, unimproved, on June 15.

In the following case a patient with patent ductus arteriosus and bacterial vegetations was pregnant. The administration of sulfanilamide was deferred until a living child was born because of the possible toxic effects of the drug on the fetus.

CASE 12—F O, a 27 year old white woman, entered the hospital on May 21, 1938. She was known to have had a cardiac lesion since childhood, having had symptoms of dyspnea on exertion, fatigability and palpitation. About three months before entry she had an acute infection of the upper respiratory tract. Since that time she had complained of weakness, malaise and headache. She entered the hospital because of a threatened miscarriage. She was in the fifth month of pregnancy. There had been no previous pregnancies.

On examination she appeared chronically ill and poorly nourished. The mucous membranes of the eyes and mouth were pale, and no petechiae were observed. On percussion the heart was found to be enlarged in the region of the pulmonary conus. A continuous thrill was felt over the left second interspace. A typical "machinery-like murmur" was heard over this area with both a systolic and a diastolic phase. The murmurs were transmitted to the left clavicle. The pulmonic second sound was accentuated. The lungs presented no abnormality. The blood pressure was 140 mm of mercury systolic and 80 mm diastolic. The fundus of the uterus reached the level of the umbilicus. The liver and spleen were not felt. There was no edema of the extremities.

Laboratory examination showed that the urine contained albumin, with erythrocytes and leukocytes in the sediment. The value for hemoglobin was 66 per cent, the erythrocyte count was 2,810,000 and the leukocyte count 18,900 per cubic millimeter of blood. *Str. viridans* was isolated from the blood on many occasions, with 1 to 181 colonies per cubic centimeter.

Roentgenologic examination of the heart showed definite enlargement of the pulmonary conus and of the right ventricle. Prior to delivery the patient was given several transfusions. She had frequent chills and was febrile. She suffered from severe pulmonary infarcts. Approximately two and one-half months after entry she had spontaneous labor, and a living child was born. Shortly after delivery, a culture of the patient's blood showed *Str. viridans*, the cord blood of the infant was sterile. After several transfusions the patient improved slightly, but she continued to have pulmonary infarcts. About one week post partum she was given sulfanilamide by mouth. The doses varied between 45 and 60 grains (2.91 and 3.88 Gm) a day. The free sulfanilamide in the blood averaged 3 mg per hundred cubic centimeters. She tolerated the drug poorly, suffering from anorexia and vomiting. She remained febrile. The bacteremia persisted. Under the circumstances, sulfanilamide therapy was discontinued, and she was sent home on September 1.

COMMENT

The primary purpose in the study of these cases was to evaluate the effect of sulfanilamide on the clinical course of subacute bacterial endocarditis. Although the number of cases is small, it appears that the drug had a definite beneficial effect on 2 of the 12 patients. In case 1 there was evidence of meningitis in addition to bacterial endocarditis. The clinical and anatomic evidence indicates that there was no residue of the acute attack of meningitis. We are not aware of any reports in the literature of cases in which sulfanilamide has been of any value in the treatment of meningitis due to *Staph albus*. Block and Pacella¹⁶ reported a case of staphylococcic meningitis in a child 17 days old, in which a cure was apparently obtained with sulfanilamide. No statement was made as to whether the organism isolated was *Staph albus* or *Staphylococcus aureus*. By permission of Dr Irvine McQuarrie and his associates, of the department of pediatrics at the University Hospitals, we had the opportunity of observing a 3 year old child who had meningitis due to *Staph albus*. Sulfanilamide was given to this patient for a long period, but the disease terminated fatally. Another child, 17 months old, had meningitis due to *Staph aureus*. He also had hydrocephalus. Administration of sulfanilamide was followed by recovery from the meningitis.

After the diagnosis of bacterial endocarditis had been established in case 1, the patient was apparently "cured" and remained so for seven months. Of considerable interest were the minimal changes observed in the endocardium at autopsy. Bacterial endocarditis was apparently engrafted on a previously normal valve. The lack of extensive damage to the mitral valve over such a long period might be explained on the basis of invasion of tissues by an organism of low virulence or by the bacteriostatic effect of sulfanilamide. It is interesting to speculate on the outcome of this patient's illness if sulfanilamide had been prescribed for a long period after her first discharge from the hospital.

At the time of writing, the second patient in this series has been in good health for nine months after sulfanilamide therapy. Whether there is only a remission in her disease or whether she is cured will be answered only by a prolonged period of observation. It is important that before sulfanilamide was given a quantitative study of blood cultures showed 30 colonies of *Sti viridans* per cubic centimeter of blood on one occasion and 200 colonies on another. In the remaining 10 cases we do not believe that sulfanilamide therapy had any desirable effect on the course of the disease.

16 Block, H., and Pacella, B. L. Staphylococcic Meningitis. Report of a Case in a Seventeen Day Old Infant Successfully Treated with Sulfanilamide, J. A. M. A. **110** 508 (Feb. 12) 1938.

There is little doubt that in some patients the administration of sulfanilamide will render the blood stream sterile, as determined by cultures of venous blood. This was true of 6 of the 12 patients in this series. However, this bactericidal effect appeared to be only temporary, except in cases 1 and 2. We observed 2 patients in whom the blood was rendered free of bacteria by sulfanilamide, but when administration of the drug was discontinued for forty-eight hours bacteremia was again established. In 6 patients the prolonged administration of sulfanilamide did not sterilize the blood. It is likely that the organisms in the vegetations are protected from the action of sulfanilamide, even though the drug may have a bactericidal effect on those that reach the blood stream. It may be that certain strains of *Str. viridans* are more readily destroyed by sulfanilamide than others. We have initiated a study of this problem.

All of the 12 patients were febrile during their illnesses. In 4 there was a definite decline of the temperature, coincident with the administration of sulfanilamide. The temperature became normal or was only slightly elevated. In 5 patients the drug did not appear to affect either the temperature or the bacteremia. The patient in case 3 had only a low grade fever throughout the period of observation, and there were only 1 to 14 colonies of organisms per cubic centimeter of blood. Yet sulfanilamide therapy had no effect on either the fever or the bacteremia. The patient in case 6 had a high fever and persistent bacteremia, neither of which was affected by sulfanilamide. In 1 patient (case 7) after sulfanilamide was given the temperature became and remained normal but the bacteremia was unaffected. In 2 patients (cases 10 and 11) sulfanilamide therapy was accompanied by sterilization of the blood, but was without effect on the temperature. We did not observe any instance of "drug fever," as described by Hageman and Blake.¹⁷

Although all the patients had some degree of anemia during their illness, in only 1 could a rapid decline in the hemoglobin and erythrocyte levels be attributed to sulfanilamide. In case 10 5 Gm. of the drug was given daily for one week. During this time the value for hemoglobin dropped from 51 to 36 per cent, and the erythrocyte count, from 2,500,000 to 1,950,000 per cubic millimeter. There was no further decline when the drug was discontinued. In no instance did sulfanilamide cause a depression of the leukocyte level. In 2 patients (cases 4 and 11) there was a definite and marked increase of the leukocytes during the administration of sulfanilamide.

¹⁷ Hageman, P. O., and Blake, F. A Specific Febrile Reaction to Sulfanilamide, *J. A. M. A.* **109** 642 (Aug. 28) 1937.

Sulfanilamide Therapy in 12 Cases of Bacterial Endocarditis

Case, Duration of Sex Symptoms and Before Age in Treatment, Years Wk	Cardiac Lesion		Causative Organism with Number of Colonies per Cc of Blood	Sulfanilamide Therapy		Time Under Observa- tion	Comment
	Cause	Anatomic Type		Total Dose, Gm	Toxic Signs and Symptoms		
1 F 35	23 Bacteria implanted on normal valve	Mitral stenosis	Staph albus, 1 to 11	185 in 15 days, 124.5 in 56 days	None on first admis- sion, nausea, vomit- ing, anorexia, loss of weight on second admission	Spinal fluid steril- ized, blood sterilized, temperature normal, Staph albus on heart valve at autopsy	Afebrile 203 days, in- gained 40 pounds in weight, had 2 remis- sion or reinfection, died, autopsy
2 F 18	8 Congenital	Patent ductus arteriosus	Str viridans 30 to 200	191.6 in 53 days	None transfusion before sulfanilamide	Blood sterilized, temperature normal	Good health 9 mo after leaving hospi- tal, cure (?)
3 F 20	5 Congenital	Patent inter- ventricular septum	Str viridans, 1 to 14	276 in 67 days	Listlessness, leth- argy, anorexia	No effect on bac- teremia or tem- perature	Discharged home, no improvement
4 F 25	16 Congenital	Patent inter- ventricular septum	Str viridans, 10	53.2 in 23 days	Nothing definite, signs of failure of right heart with jaun- dice and exanthesis	Blood sterilized while drug given bacteremia when omitted, tem- perature normal	Died 59 days after first seen, no autopsy
5 F 31	20 Congenital	Coarctation of aorta, bicuspid aortic valve	Str viridans, 100	64 in 11 days	Difficult to exsanguinate, listlessness, weakness, anorexia	Blood cultures sterile temperature approached normal, Str viridans on heart valve at autopsy	Died autopsy
6 F 23	8 Rheumatic	Mitral stenosis	Str viridans, 200	12.6 in 11 days	Nothing definite because of toxicity from disease	No effect on bac- teremia or temper- ature	Left hospital against advice died 3 mo later, no autopsy
7 M 36	12 Rheumatic	Mitral stenosis, aortic regur- gitation	Str viridans, 65	87.7 in 23 days	None	No effect on bac- teremia, normal temperature	Died 3 mo after leaving hospital, took drug at home, no autopsy
8 F 29	12 Rheumatic	Mitral stenosis	Str viridans, 300	131.6 in 31 days	Anorexia, anemia, repeated transfusions necessary	No effect on bac- teremia or temper- ature	Died, autopsy
9 M 66	10 Rheumatic	Mitral stenosis	Str viridans, 150	102.5 in 19 days	Nothing definite, toxic before sulfan- ilamide therapy	No effect on bac- teremia or temper- ature	Died, autopsy
10 M 70	8 20 ? Arterio- sclerotic	Aortic regur- gitation	Str viridans, 200	33.87 in 7 days	Severe anemia for 1 week	Blood sterilized, no effect on temperature	Died 1 wk after leaving hospital, against advice, no autopsy
11 F 40	12 Congenital	Patent ductus arteriosus	Str viridans, 100	267 in 58 days	Listlessness, leth- argy, anorexia	Blood sterilized, bac- teremia when drug omitted no effect on temperature	Discharged home, no improvement
12 F 27	12 Congenital	Patent ductus arteriosus	Str viridans, 1 to 181	95.8 in 36 days	Anorexia, vomiting	No effect on bac- teremia or temper- ature	Pregnant, delivered of living premature baby, sulfanilamide after delivery, dis- charged home, no improvement

The level of free sulfanilamide in the blood of these patients was determined at frequent intervals. We could find no definite relation between the amount present in the blood and its effect on the bacteremia. The highest level was 18.3 mg per hundred cubic centimeters (case 9). In the patient who was apparently cured (case 2) the sulfanilamide level varied between 5.3 and 8.5 mg per hundred cubic centimeters. In 1 patient the blood cultures remained sterile when the sulfanilamide level of 3.1 mg per hundred cubic centimeters was reached. Tests in vitro showed that sulfanilamide had a marked bacteriostatic effect on the organisms in this case. Another patient continued to have bacteremia with a level of 10.6 mg of sulfanilamide per hundred cubic centimeters of blood.

Difficulty was experienced in evaluating the toxic effects of the drug because the disease itself complicated the symptoms. A majority of the patients had anorexia during the administration of sulfanilamide. This was so severe in some of the patients that the drug had to be discontinued. The patients also appeared listless and lethargic in varying degrees while taking the drug. It is of considerable interest that none of the patients exhibited more than a slight degree of cyanosis. The carbon dioxide-combining power of the patients' blood was observed at frequent intervals, and no patient had acidosis. One patient (case 1) had nausea and vomiting due to the drug after she had taken it for several weeks. Anorexia and vomiting were prominent features in the illness in case 2, and sulfanilamide had to be discontinued because of these symptoms.

SUMMARY

Sulfanilamide was administered to 12 patients with subacute bacterial endocarditis. The etiologic agent was *Str. viridans* in 11 patients and *Staph. albus* in 1. Of the 2 patients who appeared definitely improved after receiving the drug, 1 eventually died of the disease, and at the time of writing the other has been well for nine months.

All the patients had bacteremia. Sulfanilamide rendered the blood stream sterile in 6 of the 12 patients. This bactericidal effect appeared to be only temporary, except in 2 patients.

In 4 patients there was a decline in the temperature coincident with the administration of sulfanilamide. There did not appear to be any relation between the degree of fever and the therapeutic effect of sulfanilamide.

Although the drug was taken for a long period by several of the patients, there was a marked decline in the erythrocyte level in only 1 case. In none was a depression of the leukocytes observed.

There was no definite relation between the amount of free sulfanilamide in the blood and the effect of the drug on the bacteremia.

The use of sulfanilamide in the treatment of patients with subacute bacterial endocarditis is of doubtful value because of the nature of the focus of infection

CONCLUSION

It appears from the foregoing observations that the administration of sulfanilamide to patients with subacute bacterial endocarditis will in some instances render the circulating blood free of organisms. Except for 2 of the patients, this bactericidal effect was only temporary and depended on the continued use of the drug. In 2 patients definite improvement followed the use of sulfanilamide. However, we believe that sulfanilamide and its related compounds will be of doubtful value in the treatment of patients with subacute bacterial endocarditis because of the very nature of the focus of infection. The proliferating mass of bacteria situated well beneath the surface of the vegetation is probably protected, at least in part, from the action of free sulfanilamide in the blood, as well as of specific antibodies. When the organisms approach the surface of the vegetation, they are carried off in the circulating blood, and under these circumstances may be killed. An analogous therapeutic situation is now recognized in the treatment of patients with bacteremia due to beta hemolytic streptococci. Lockwood¹⁸ stated that in a number of instances of infection of the blood stream an infected thrombus in a large vessel has prevented satisfactory elimination of the bacteremia.

Since the presence of sulfanilamide in the blood may have a bacteriostatic effect on some strains of *Str. viridans*, sulfanilamide probably should be administered to any patient with valvular lesions who may be subjected to oral surgical procedures. It is well known that after the extraction of teeth or after a tonsillectomy temporary bacteremia with *Str. viridans* may result.

18 Lockwood, J. S. Observations on the Mode of Action of Sulfanilamide and Its Application to Surgical Infections, *Ann Surg* 108 801 (Nov) 1938

MYOCARDIAL INFARCTION WITHOUT SIGNIFICANT LESIONS OF CORONARY ARTERIES

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Since Heberden's¹ famous description of the clinical syndrome of angina pectoris and the subsequent finding of associated calcification of the coronary arteries by Jenner² and his pupil Parry,³ the controversy about the etiologic role of narrowing of the coronary arteries in Heberden's syndrome has never ceased to hold interest. Until recently all objections have been based on the frequent disparity between the anatomic and the clinical features. The difficulty in correlating morbid anatomy, on the one hand, with disturbed physiology, on the other, has been epitomized by Aschoff.⁴ Similar discrepancies between the location and size of the myocardial infarction and the corresponding vascular lesion have been indicated.

The occurrence of major myocardial damage with a minimum or even absence of coronary disease is not rare. S. A. Levine⁵ cited 11 of his own cases studied at autopsy in which major myocardial lesions were accompanied by corresponding disease of the coronary arteries. In a study of 100 cases of myocardial infarction Lisa and Ring⁶ found 8 in which the lesions in the vessels were minimal or the vessels were normal. Barnes and Ball,⁷ Brown,⁸ Davenport⁹ and others observed

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1 Heberden, W. Some Account of a Disorder of the Breast, *Med Tr Roy Coll Phys London* 2: 59, 1786

2 Jenner, E., cited by Parry³

3 Parry, C. H. An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris, London, Cadell & Davis, 1799

4 Aschoff, L., and Tawara, S. Die heutige Lehre von der pathologisch-anatomischen Grundlagen der Herzschwache, Jena, Gustav Fischer, 1906

5 Levine, S. A. Coronary Thrombosis, Baltimore, Williams & Wilkins Company, 1929

6 Lisa, J. R., and Ring, A. Myocardial Infarction or Gross Fibrosis. An Analysis of One Hundred Necropsies, *Arch Int Med* 50: 131 (July) 1932

7 Barnes, A. R., and Ball, R. G. The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am J M Sc* 183: 215, 1932

(Footnotes continued on next page)

instances of myocardial infarction without complete coronary occlusion Krumbhaar and Crowell¹⁰ reported cases of arteriosclerotic heart disease associated with rupture of the myocardium in areas where the coronary arteries were patent. Several interesting cases are recorded by Jaffé and Bross¹¹. These were instances of sudden death due to rupture of the left ventricle in which the coronary vessels were normal, but microscopically there were numerous areas of focal necrosis. They concluded that the lesions were due to an acute circulatory disturbance. V. Levine¹² studied cases of diffuse myocardial fibrosis with patency of the coronary arteries, but in these cases frank infarction was not present.

Our study adds 15 new instances of extensive myocardial infarction in which the intimal changes in the coronary arteries were insignificant and the lumens not materially narrowed. It is our intention in this paper to consider the functional factors which could produce circulatory disturbances severe enough to cause necrosis of the cardiac muscle even though the lumens of the coronary arteries remained patent.

There were 8 men and 7 women, the ages ranging from 41 to 78. Five of the patients had an anginal syndrome, 5 others had a history of dyspnea on exertion without anginal pain, 1 had rheumatic heart disease and 4 had no symptoms referable to the heart.

Hypertension was frequent. Blood pressure readings of 150 systolic and 90 diastolic were accepted as the upper limits of normal. A definite history of hypertension was obtained in 9 of the 15 cases. In 4 others, hypertension was probable in view of the marked cardiac hypertrophy not explained by other causes. In 1 case the blood pressure was elevated, though the heart weighed 340 Gm. It is obvious from either the elevated blood pressure or the increased heart weight that the majority of our cases, 13 of 15, were most likely instances of present or antecedent hypertension. The very fact that this type of myocardial damage with a small or no vascular lesion occurs so frequently with hypertension is itself of striking interest.

Cardiac hypertrophy was deemed to have existed when the heart weighed 350 Gm or more or when microscopic slides showed generalized fibrous hypertrophy in a heart weighing less. While this figure is in some measure arbitrary, it is generally accepted as the upper limit of normal. In 12 cases the heart weighed 350 Gm or more.

8 Brown, M. R. A Study of the Pathogenesis of Myocardial Fibrosis ("Chronic Fibrous Myocarditis"), *Am J M Sc* **184** 707, 1932.

9 Davenport, A. B. Spontaneous Heart Rupture—A Statistical Summary, *Am J M Sc* **176** 62, 1928.

10 Krumbhaar, E. B., and Crowell, C. Spontaneous Rupture of the Heart, *Am J M Sc* **170** 828, 1925.

11 Jaffé, R., and Bross, K. Histologische Befunde bei Herzrupturen, *Centralbl f allg Path u path Anat* **56** 246, 1933.

12 Levine, V. Myocardial Changes in Hypertension, *Arch Path* **18** 331 (Sept) 1934.

Congestive heart failure was present in 7 cases and varied in duration from three months to seven years. The average weight of the heart in cases of chronic congestive heart failure was 587 Gm. The

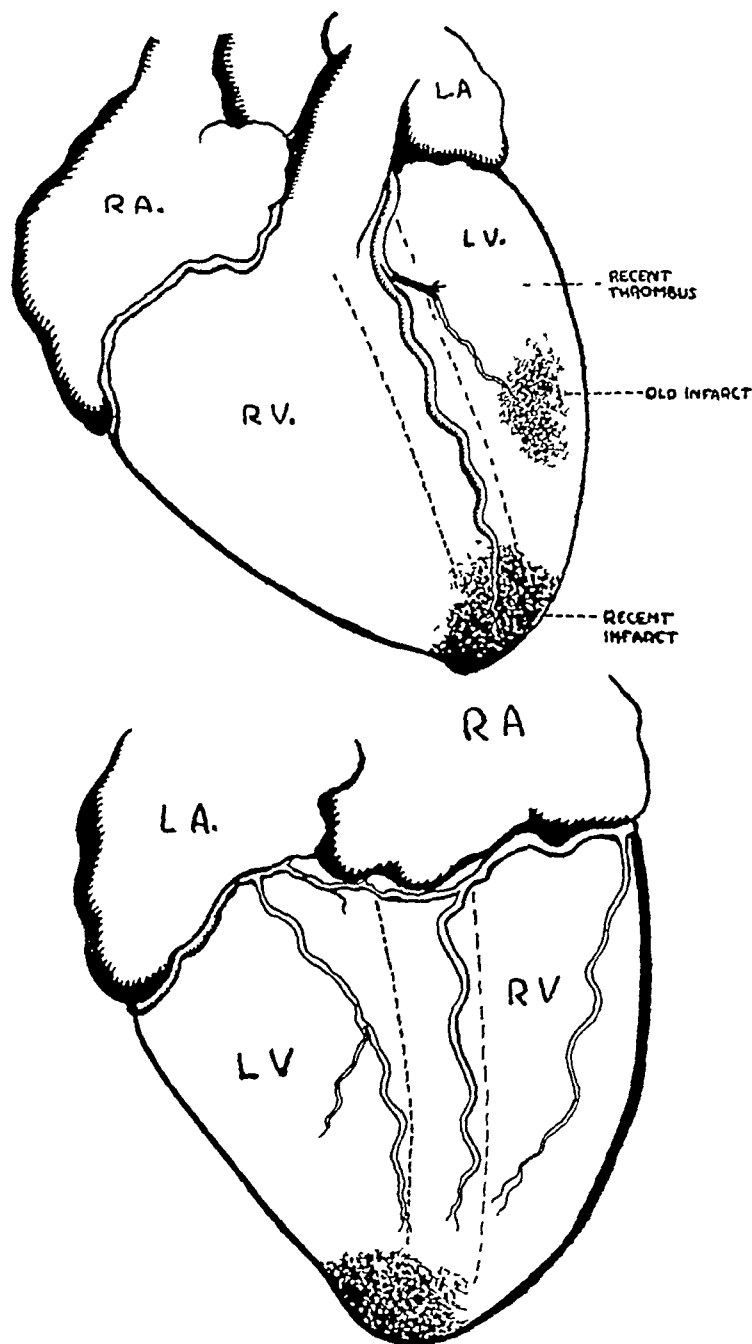


Fig 1 (case 13) —Anterior and posterior view of the heart, which weighed 810 Gm

average weight in cases in which there was no congestive heart failure was 367 Gm. Myocardial damage was common to both groups, only patients with failure had great cardiac enlargement.

CORONARY ARTERIES

In our 15 cases the vessels, in general, showed only a slight degree of arteriosclerosis, with good-sized lumens in all. The condition of the coronary arteries was comparable to that of a normal group of persons of similar ages. The need for thorough anatomic dissections in such cases is apparent. If the vessels are opened lengthwise, it is conceivable that a small thrombus may be dislodged and pushed aside. If the vessels are transected, a small occlusion may be overlooked unless the sections are made at minute intervals. In our series the blood vessels were sectioned transversely and checked by microscopic sections of different portions of the heart. In 4 of the hearts, we made extremely minute

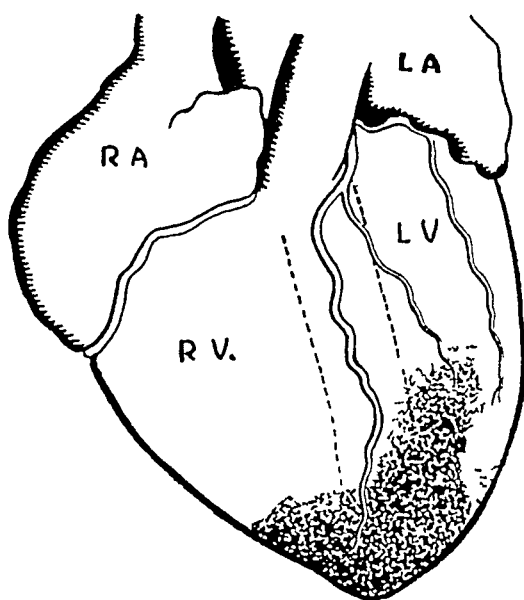


Figure 2

Fig 2 (case 14) —Anterior view of the heart, which weighed 480 Gm

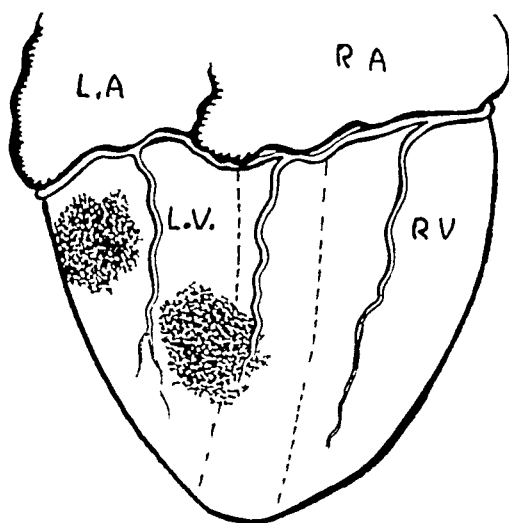


Figure 3

Fig 3 (case 15) —Posterior view of the heart, which weighed 290 Gm

dissections of the coronary arteries before and after fixation. In 1 case serial sections of the entire major arterial tree were cut. In all our cases vascular involvement was slight. In no instance was there appreciable narrowing of the coronary arteries.

In some hearts occasional small intimal plaques were encountered. Microscopically these showed the usual changes, with fibrosis and lipid-laden mononuclear cells. Occasional minute areas of calcification were found. The lumens, however, were nowhere significantly reduced, and there was no evidence of recanalization, intimal hemorrhage or arteritis at any point. The case in which serial sections were made is particularly pertinent. The vessels throughout their course were elastic and collapsed, and arteriosclerosis was minimal.

MYOCARDIAL INVOLVEMENT

Of the 15 patients, 1 showed acute myocardial infarction, while the 14 others showed healed myocardial infarction. The localization of myocardial lesions in this group followed, in general, the same areas of predilection observed in patients with coronary sclerosis and thrombosis. The left ventricle was most frequently involved, namely, in 14, and the right ventricle was involved in 1. The area usually supplied by the anterior descending ramus of the left coronary artery was the most frequent site.

The sites of infarction and fibrosis were as follows:

	No of Cases		No of Cases
Infarction of posterior wall	1	Interventricular septum and papillary muscle	1
Infarction of posterior wall, fibrosis of left ventricle	1	Interventricular septum and apex of left ventricle	1
Infarction at apex	3	Septum and anterior and posterior walls of right ventricle	1
Infarction at apex, diffuse fibrosis	1	Septum, apex, anterior (old) and posterior (recent) walls	1
Infarction at apex, diffuse fibrosis with aneurysmal dilatation	1	Apex, left ventricle and septum	1
Posterior wall of right ventricle	1	Anterior and posterior walls and septum	1
Interventricular septum	1		

The coronary arteries were essentially normal.

VALVULAR INVOLVEMENT

One patient had arteriosclerotic aortic insufficiency and stenosis. Another had mitral stenosis and insufficiency and aortic insufficiency of rheumatic origin. A patient not reported on in this study had rheumatic aortic insufficiency with myocardial infarction of the posterior wall of the left ventricle.

COMMENT

The basic physiologic factor in angina pectoris and coronary disease as has been maintained by Rothschild and Kissin,¹³ Keefer and Resnik¹⁴ and others, is a state of imbalance between the myocardial need of oxygen and the supply of oxygen. This imbalance, depending on its severity and its duration, may lead to different phenomena, varying from transitory anginal pain to extreme myocardial damage. In its severest form it may lead to sudden death with or without myocardial infarction.

13 Rothschild, M. A., and Kissin, M. Anginal Syndrome Induced by Gradual General Anoxemia, *Proc Soc Exper Biol & Med* **29** 577, 1932.

14 Keefer, C. S., and Resnik, W. H. Angina Pectoris. A Syndrome Caused by Anoxemia of the Myocardium, *Arch Int Med* **41** 769 (June) 1928.

Clinical and Pathologic Data in Fifteen Cases of Myocardial Infarction Without Significant Lesions in the Coronary Arteries

Case Sex Age	Cardiac Weight, Gm	Blood Pressure	Symptoms and Signs	Pathologic Data
1 M 70	340	185/190/85	Diabetes mellitus 20 yr amputation of right leg 2 yr before admission gangrene of left foot 2 mo no anginal pain no congestive heart failure sudden death probably due to cardiac failure	Superficial atheromas of coronary arteries with slight calcification lumens of good size throughout healed infarct of posterior wall of left ventricle diffuse fibrosis of left ventricle arteriosclerotic gangrene of left leg thrombosis of iliac arteries
2 F 63	380	145/80	Headaches, 1 yr right hemiplegia 1 mo hepato megal and splenomegaly no history of anginal pain or congestive failure poly cythaemia vera death from bronchopneumonia	Moderate coronary atherosclerosis lumens of good size throughout healed infarct of apex of left ventricle splenomegaly thrombosis of adrenal and pituitary veins
3 F 48	270	100/65	Carcinoma of cervix with metastasis to lumbar portion of spine and brain tachycardia extrasystoles no anginal pain or congestive heart failure died in uremia	Occasional intimal plaques in coronary arteries 2 healed infarcts at middle of posterior wall of left ventricle largest measuring 1.5 by 1.5 by .5 cm papillary cystadenoma of ovary with metastasis arteriosclerosis of kidneys uremia
4 F 41	350	150/80	Collapsed in anginal seizure shortly thereafter dyspnea and edema of legs advanced congestive failure 3 mo death due to bronchopneumonia	Slight coronary atherosclerosis lumens of good size throughout infarct of apex of left ventricle with mural thrombosis cardiac hypertrophy and dilatation thrombi in both auricles chronic passive congestion of viscera ascites healed infarcts of spleen and kidney
5 M 52	350	140 156/90 110	Right hemiplegia 8 yr pain in left hypochondrium heaviness and discomfort 3 yr dyspnea on exertion, 4 yr polycythaemia vera hepatic and splenic enlargement not in congestive heart failure electrocardiogram showed prominent Q ₁ and Q ₂ T ₁ inverted T ₂ flat T ₃ low voltage death from cerebral insult	Few small atheromatous areas in coronary arteries with no encroachment on lumens healed infarct of apex of left ventricle with aneurysmal dilatation and mural thrombus diffuse fibrosis of both ventricles chronic passive congestion of viscera splenomegaly healed and recent splenic infarcts massive infarction of adrenals duodenal ulcer arteriosclerosis of kidneys
6 M 54	750	170/120	Headaches 20 yr dyspnea on exertion and cardiac asthma 1 yr no anginal pain advanced congestive heart failure 7 yr death from cerebral insult	Small plaques scattered in coronary arteries lumens widely patent throughout healed infarct of apex of left ventricle 1.5 cm in diameter small patches of fibrosis elsewhere hydrothorax hydro pericardium healed and recent infarcts of spleen arteriosclerosis of kidneys
7 F 44	520	154 160/90	Rheumatic fever at 14 and again 6 mo before admission mitral stenosis and mitral insufficiency auricular fibrillation left hemiplegia advanced congestive heart failure, 4 yr anginal pain, 2 mo electrocardiogram showed small Q ₁ inverted T ₂ and T ₃ sudden death	A few small plaques in coronary arteries lumens widely patent everywhere- healed infarcts at upper portion of posterior wall of left ventricle, 3.5 cm in diameter and at lower portion of intraventricular septum and anterior two thirds of left ventricle old and recent rheumatic endocarditis of mitral and aortic valves mural thrombi of auricular appendage healed infarcts of spleen and kidneys cerebral embolism
8 F 77	500	145/80	Weakness dyspnea and edema of extremities 5 yr no history of angina pectoris death from progressive congestive heart failure	A few atherosclerotic plaques in coronary arteries lumens of good size throughout healed infarct of apex of left ventricle 4 by 3 cm atherosclerotic aortic insufficiency and stenosis bilateral hydrothorax generalized arteriosclerosis
9 M 78	800	136/70 Hypertension known 2 yr	Left hemiplegia 2 yr before admission several anginal attacks in 2 mo death from progressive congestive failure	Moderate sclerosis at mouths of coronary arteries a few small plaques in widely patent vessels healed infarct of apex of left ventricle involving interventricular septum emphysema generalized arteriosclerosis

Clinical and Pathologic Data in Fifteen Cases of Myocardial Infarction Without Significant Lesions in the Coronary Arteries—Continued

Case, Sex Age	Cardiac Weight, Gm	Blood Pressure	Symptoms and Signs	Pathologic Data
10 M 49	600	150-220/110-130	Dyspnea and cough, 7 yr congestive failure 5½ yr auricular fibrillation no anginal pain electrocardiogram showed inverted T ₁ flat T ₂ high RT ₃ transition slurring of QRS PR interval 0.24 sec sudden death	A few atheromatous plaques in larger branches of coronary arteries lumens patent throughout healed infarct of posterior wall of right ventricle, 1.5 cm from apex measuring 4 by 4.5 cm ascites bilateral hydrothorax generalized arteriosclerosis and renal arteriosclerosis
11 F 59	470	132/90	Dyspnea, 6 mo senile psychosis no anginal pain or congestive failure electrocardiogram showed inverted T ₁ high take off of T ₂ and T ₃ slurring of all QRS complexes intraventricular conduction disturbance auricular fibrillation sudden death	Coronary arteries thinly atheromatous and patent throughout healed infarct of interventricular septum and apex of left and right ventricles, pulmonary infarcts, renal arteriosclerosis and arteriosclerosis diffuse arteriosclerosis bilateral fibroid tuberculosis with cavitation
12 M 62	350	115/70	Pain and burning in left leg 6 yr severe pain in right side of chest and back 6 mo no congestive failure electrocardiogram showed auricular fibrillation low take off of T ₁ and T ₂ which were inverted death from gangrene of left leg	Very slight atherosclerosis of coronary arteries which were patent throughout healed infarct of interventricular septum near apex, 1.5 cm bilateral pulmonary tuberculosis with cavitation thrombosis of left common iliac artery gangrene of left leg
13 M 75	810	160/105	Edema of ankles 5 yr no history of angina pectoris congestive heart failure, 5 yr exact cause of death not known had infection of arm recent occlusion of small coronary artery and ulcers of duodenum	Moderate sclerosis of first 3 cm of left anterior descending coronary artery lumen of good size throughout small branch of left anterior descending artery given off 3 cm from origin extended diagonally along left ventricle and was occluded by a recent thrombus right coronary artery showed slight atherosclerosis with lumen of good size throughout recent infarction of apex anterior and posterior wall of left ventricle and septum, 5 by 4 cm mural thrombus old infarct of anterior wall of left ventricle 5 by 6 cm recent occlusion near old infarct recent infarct not related to recent occlusion which was very small infarct of spleen arteriosclerotic aneurysm of splenic artery arteriosclerosis of kidneys multiple subacute ulcers of duodenum cerebral arteriosclerosis (fig 1)
14 F 57	450	136/110	Angina pectoris, 2 or 3 yr anorexia nausea vomiting and dyspnea on exertion 7 mo no congestive failure Grawitz tumor of left kidney with metastasis sudden death	Slight thickening of walls of first portion of major branches of coronary arteries walls elastic and lumens widely patent throughout areas of thinned out myocardium in anterior and posterior walls of left ventricle old large infarct of septum except for upper 5 cm extending to anterior and posterior walls of left ventricle and portion of right ventricle near septum hypertrophy and dilatation of heart Grawitz tumor of left kidney fibromas of uterus left ovary and stomach (fig 2)
15 M 62	290		Weakness anorexia and cough for 1 yr severe anemia no history of angina pectoris or congestive failure	Coronary arteries thin walled and elastic lumens widely patent left circumflex branch on posterior wall of narrow caliber but thin and elastic wall no occlusion 2 old infarcts on posterior surface of left ventricle including posterior papillary muscle hypernephroma of right kidney with metastasis to left kidney, adrenals lungs brain and epicardium (fig 3)

The physiologic mechanisms whereby this delicate balance of oxygen need and supply is maintained are widespread and complex. The heart is a continuously functioning organ. Further, it is unique in that its nourishment depends on the coronary flow which it must itself supply. Its crucial situation is expressed by the wide variety of physiologic phenomena, both cardiac and extracardiac, which, with few exceptions, are directed toward increasing its blood supply rather than to yielding blood for purposes elsewhere. Its nourishment and proper function depend on reflex and humoral factors involving many organs, including the proper surrendering of blood by the depot organs, the liver, spleen and skin.

Failure of any of these compensatory mechanisms may initiate myocardial anoxia. Such failure may account not only for the cases of extreme infarction with minimal coronary disease, such as we have reported, but for the frequently observed discrepancy between the degree of vascular disease and the condition of the myocardium. It is worth while therefore to review these physiologic mechanisms, failure of which may produce myocardial ischemia in the absence of obvious vascular occlusion.

Factors Affecting Myocardial Nutrition

I Mechanical Factors

- 1 Fall in aortic blood pressure, especially in peripheral shock
- 2 Phasic variations in coronary flow
 - Aortic insufficiency, arteriovenous fistula
 - Aortic stenosis
 - Hypertension
- 3 Cardiac hypertrophy
- 4 Tachycardia
- 5 Failure of adequate collateral circulation, anomalies of coronary arteries

II Changes in Blood

- 1 Anemia
- 2 Polycythemia

III Reflex Factors

(A) Coronary Vasomotor Reflexes

Anoxemia due to

- (a) Failure of compensatory dilatation due to
 - 1 Inadequate reflex response
 - 2 Sclerosis of vascular walls
- (b) Marked vasoconstriction

These reflexes may be classified as

- 1 Reflexes originating in heart and associated structures
 - (a) Proprioceptive reflexes adapting coronary flow to increased work, etc
 - (b) Carotid sinus reflexes
- 2 Reflexes originating in different parts of body, especially
 - (a) Those arising in abdominal viscera
 - (b) Pulmocoronary reflex

3 Reflexes originating centrally

(B) Extracardiac Reflexes Affecting Coronary Flow

Failure of adequate emptying of depot organs (liver, spleen, skin, etc.)

1 Digestive state

2 Variations in temperature

3 Relaxed abdominal musculature

IV Humoral Factors

1 Epinephrine

2 Histamine

3 Acetylcholine

4 Vasopressin, etc

MECHANICAL FACTORS

1 *Fall in Aortic Blood Pressure*—In the denevated heart-lung preparation of the dog an increase in the mean blood pressure from 50 to 130 mm of mercury may increase the coronary flow from 20 to 250 cc per minute¹⁵. Conversely, a marked fall in the head pressure in the aorta will cause a great decrease in the coronary flow. A reduction of the coronary flow resulting from a severe fall in the aortic pressure may produce anginal pain and, conceivably, myocardial infarction from anoxia. Saphir and his co-workers¹⁶ believe such falls of intra-aortic blood pressure to be a causative factor of myocardial damage in a heart in which the muscular damage is greater than the associated coronary disease.

Similarly, peripheral shock associated with a fall in the aortic head pressure may seriously impair the coronary flow. In surgical shock, paralytic ileus and other states of peripheral failure, anginal pain and coronary thrombosis are not uncommon occurrences. In many cases, furthermore, the cardiac symptoms appear for the first time. At necropsy the myocardial damage is often greater than the associated coronary arteriosclerosis. While direct clinical evidence is difficult to obtain, experimental evidence supports the view that shock may be a causative factor in cardiac ischemia. If a guinea pig is strapped upright to a board, collapse results owing to pooling of blood in the abdomen and lower extremities¹⁷. Electrocardiograms taken at this time show evidence of myocardial damage, and histologic examination reveals multiple necrotic areas in the myocardium, especially in the septum and papillary muscles of the left ventricle. Similar changes have been observed in guinea pigs after doses of histamine sufficient to cause collapse.

15 Wright, S. Applied Physiology, ed 5, New York, Oxford University Press, 1934.

16 Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N. Coronary Thrombosis and the Resulting Myocardial Changes, *Am Heart J* 10 567, 1935.

17 Meessen, H. Ueber Coronarinsuffizienz nach Histamincollaps und nach orthostatischem Collaps, *Beitr z path Anat u z allg Path* 99 329, 1937.

2 Phasic Variations in the Coronary Flow—Aside from the mean aortic pressure, phasic variations in the coronary flow during both systole and diastole are of the utmost importance¹⁸ In the normal heart the coronary flow is greater during diastole, since this is the longer phase of the cardiac cycle¹⁹ Furthermore, the resistance to flow in the coronary arteries arises during systole, as the intramural coronary arteries are compressed by the contracting cardiac muscle However, even in the normal heart the systolic coronary flow is important, and in pathologic states in which the diastolic pressure is decreased, the systolic coronary flow may provide the major nutrition of the heart²⁰

H D Green²⁰ has shown experimentally that in conditions associated with low diastolic blood pressure, such as aortic insufficiency and arteriovenous fistula, the coronary flow is greatly diminished owing to the low aortic diastolic pressure This decrease is partly compensated for by elevation of the systolic pressure An increase in the systolic pressure results in two divergent effects The increased aortic pressure tends to increase the coronary flow, whereas increased compression of the intramuscular arteries tends to decrease the coronary flow However, as the systolic pressure is raised, the former outweighs the latter, and the coronary flow is increased The systolic coronary flow may be increased to double that occurring normally during diastole In patients with compensated aortic insufficiency, an adequate coronary flow is maintained by reflex peripheral vasoconstriction which elevates the systolic pressure Failure or inadequacy of this compensatory mechanism may initiate severe myocardial anoxemia

In aortic stenosis the coronary flow is reduced chiefly during systole Because of the high intraventricular pressure during systole, there is marked compression of the intramuscular coronary arteries, so that the coronary flow is impeded In contradistinction to aortic insufficiency, peripheral vasoconstriction would not be a compensatory mechanism A reflex reduction of the cardiac rate would, however, augment the coronary flow by prolonging the diastole

Probably the incidence of anginal attacks in young rheumatic patients is related to these phenomena If the impairment of nutrition is great enough, particularly if there is superadded arrhythmia, the result of disturbances of reflex control, even a fatal outcome, is not uncommon in association with unobstructed coronary arteries

18 Gregg, D E, Green, H D, and Wiggers, C J Phasic Variations in Peripheral Coronary Resistance and Their Determinants, *Am J Physiol* **112** 362, 1935

19 Anrep, G V, and Segall, H N The Regulation of the Coronary Circulation, *Heart* **13** 239, 1926

20 Green, H D Coronary Blood Flow in Aortic Stenosis, in Aortic Insufficiency and in Arterio-Venous Fistula, *Am J Physiol* **115** 94, 1936

In hypertensive patients, the diastolic and to a lesser extent the systolic coronary flow are augmented by increased systolic and diagnostic pressures²¹ The benefit of an increased systolic and diastolic coronary flow is, however, evanescent, since the underlying cause persists and requires the heart to do an increased amount of work

3 *Cardiac Hypertrophy*—Cardiac hypertrophy may result also in impairment of nutrition owing to the increased amount of tissue nourished by the given vascular bed In addition, the fiber is thicker than normal Hill²² showed that the rate of diffusion of oxygen varies inversely as the square of the distance Gross and Spark²³ observed an inverse ratio between the number of capillaries and the thickness of the fiber The part of the fiber nearest a capillary will receive ample blood, while the innermost part of the fiber will suffer from anoxia Harrison²⁴ demonstrated that in various species of animals the heart rate is in inverse proportion to the size of the cardiac fiber but that in the hypertrophied heart the pulse rate is not proportionately slowed It has, furthermore, been shown that for a given minute volume, the consumption of oxygen is greater per beat but less per minute at slow than at fast pulse rates²⁵ In the thickened fiber, unless diastole is prolonged by a slow pulse rate, anoxia of the cardiac muscle readily develops Since the oxygen need is greater, the nutritional reserve in the hypertrophied heart is less than that in the normal heart It is understandable, therefore, that in the enlarged heart with an impaired nutritional reserve, ischemia from any cause may result in myocardial failure, while in the small heart, only transitory anginal pain will occur

4 *Tachycardia*—In tachycardia the coronary flow diminishes owing to shortening of the diastole Gregg²¹ showed that the systolic flow is also reduced by tachycardia owing to abbreviation of the systole as well as to increased intiamural resistance In experimental hyperthyroidism and mechanically induced tachycardia, Menne, Jones and Jones²⁶ noted a parallelism between the increased heart rate and the myocardial lesions

21 Gregg, D E Phasic and Minute Coronary Flow During Acute Experimental Hypertension, *Am J Physiol* **114** 609, 1936

22 Hill, A V Diffusion of Oxygen and Lactic Acid Through the Tissues, *Proc Roy Soc, London, s B* **41** 104, 1929

23 Gross, H, and Spark, C Coronary and Extracoronary Factors in Hypertensive Heart Failure, *Am Heart J* **14** 160, 1937

24 Harrison, T R, Ashman, R, and Larson, R M Congestive Heart Failure Relation Between the Thickness of the Cardiac Muscle Fiber and the Optimum Rate of the Heart, *Arch Int Med* **49** 151 (Jan) 1932

25 Patterson, S W, and Starling, E H On the Mechanical Factors Which Determine the Output of the Ventricles, *J Physiol* **48** 356, 1914

26 Menne, F R, Jones, O N, and Jones, N W Changes in the Myocardium of Rabbits from Augmenting the Heart Rate Mechanically and from Induced Hyperthyroidism, *Arch Path* **17** 233 (March) 1934

In the hypertrophied heart with a limited oxygen and nutritional reserve, tachycardia will produce failure and more marked myocardial damage than in the normal-sized heart. Conversely, the bradycardia seen in some hypertensive patients probably acts as a compensatory mechanism to increase the coronary flow during diastole.

CHANGES IN THE BLOOD

Anemia also causes a compensatory tachycardia and frequently cardiac dilatation. The circulation time is simultaneously shortened. From severe anemia, however, myocardial fibrosis has been known to develop. Buchner and von Lucadou²⁷ showed that if an animal is rendered anemic by bleeding and then exercised, myocardial fibrosis is more diffuse and electrocardiographic changes are more marked than if the animal is only bled. The occurrence of tigering, fatty infiltration of the myocardium and fibrosis in severe anemia is direct evidence of local want of oxygen.

Polycythemia may produce anoxemia owing to oxygen unsaturation, an increased number of cells and increased viscosity. The tendency for thrombosis to develop in this disease is well known.

REFLEX FACTORS

Despite considerable experimental work, there is no unanimity of opinion concerning the mechanism or the importance of the reflex control of the coronary arteries. This is in part due to the technical difficulty of dissociating vasomotor effects from such factors as heart rate and blood pressure, which also influence the coronary flow. Other factors are the dependence of the reaction on the severity of the stimulus and the fact that different parts of the same coronary vessel vary as to reaction.

When the oxygen need of the myocardium is increased, failure of compensatory reflex dilatation may lead to insufficiency of the oxygen supply. Such failure may result from two situations. 1. The compensatory reflex may for some reason fail to occur or may be inadequate or pathologic changes, such as sclerosis, in the vascular wall may prevent adequate dilatation. 2. In addition to failure of compensatory dilatation, vasoconstriction or its extreme form spasm may play a role in the production of myocardial ischemia. Although most vasomotor coronary reflexes produce dilatation, it is conceivable that in certain pathologic states, reflex spasm may occur.

²⁷ Buchner, F., and von Lucadou, W. Elektrokardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimenteller Coronarinsuffizienz, *Beitr z path Anat u z allg Path* **93** 169, 1934.

Ricker²⁸ has assumed that the terminal vascular segments form more or less autonomous functional units which react typically to nervous impulses. Weak stimulation produces vasodilatation, medium stimulation produces vasoconstriction and strong stimulation produces excessive vasodilatation and paralysis, while the proximal portions of the arteries remain constricted or the entire vessel becomes dilated. In the highest degree this mechanism leads to stasis, during which the circulation is actually at a standstill. During this state necrosis of the involved portion of the organ may conceivably occur. Lange²⁹ demonstrated complete paralysis of arterial segments following strong electrical stimuli and stasis in the vasa vasorum of the adventitia resulting in necrosis of the musculature of the media. He demonstrated intimal proliferation in the poststatic period following exudation.

Coronary Vasomotor Reflexes—1 Reflexes Originating in the Heart and Associated Structures. Important vasomotor reflexes adapt the coronary flow to the increased work of the heart. Such proprioceptive reflexes originating in the heart and great vessels produce coronary dilatation probably by vagal inhibition and are especially important in adapting the coronary flow to the increased physical work and to cold. That vagal inhibition is the cause of such dilatation is proved by the fact that the effect is lost after vagotomy but not after stellate ganglionectomy.¹⁹ The reaction makes possible an increase of the minute flow and is independent of changes in the diastolic blood pressure. Failure of this reflex mechanism could conceivably produce myocardial ischemia.

An increased cerebral blood supply, according to Anrep and Segall,¹⁹ results in a decreased coronary flow. This reflex, according to Stella,³⁰ is governed by the carotid sinus. Reduction of the carotid sinus pressure augments the coronary flow.

2 Reflexes Originating in Different Parts of the Body. A variety of vasomotor coronary reflexes originate in widely distributed regions of the body. C. W. Greene³¹ has studied these reflexes and has mentioned the universality with which stimulation in different parts of the body produces coronary dilatation. Mild stimulation and stimulation within physiologic limits result in coronary dilatation, with vasocon-

28 Ricker, G. *Pathologie als Naturwissenschaft—Relationspathologie—für Pathologen, Physiologen, Mediziner und Biologen*, Berlin, Julius Springer, 1924.

29 Lange, F. *Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose*, Virchows Arch f path Anat **248** 463, 1924.

30 Stella, G. *Some Observations on the Effect of Pressure in the Carotid Sinus upon the Arterial Pressure and upon the Coronary Circulation*, J Physiol **73** 45, 1931.

31 Greene, C. W. *Control of the Coronary Flow by Reflexes Arising in Widely Distributed Regions of the Body*, Am J Physiol **113** 399, 1935.

striction elsewhere Wiggers³² concluded that these somatic and visceral reflexes represent a provision for reducing the coronary resistance in conditions like pain and injury which would otherwise lower the blood pressure and decrease the coronary flow Greene³¹ has also noted that coronary vasomotor reflexes are often diphasic, so that the initial reflex dilatation may be followed later by constriction An exaggerated constrictor response following dilatation may easily lead to cardiac ischemia It is noteworthy that profound stimulation directly leads to marked coronary constriction which is independent of general systemic vascular reactions Such responses must be regarded as pathologic

Of particular interest are coronary vasoconstrictor reflexes originating in abdominal viscera Disease of abdominal viscera, especially the gallbladder, is often accompanied clinically by an anginal syndrome Occasionally the anginal syndrome as well as electrocardiographic signs disappear after cholecystectomy Similarly, diaphragmatic hernia at the hiatus, as von Bergmann³³ has shown, often produces a clinical picture of coronary disease The anginal symptoms probably represent true myocardial anoxia secondary to stimulation of an abdominal viscus Sudden death, which sometimes occurs, may be due to cardiac standstill resulting from extreme vagal stimulation, but it is also possible that such vagal stimulation may produce reflex coronary vasoconstriction and myocardial ischemia

Scherf and Schonbrunner³⁴ and others show that strong stimuli originating in the lungs, such as those in pulmonary embolism, may give rise to the so-called pulmocoronary reflex, resulting in cardiac ischemia from reflex coronary vasoconstriction Hochrein and Keller³⁵ demonstrated that in pulmonary embolism there is a diminished outflow from the right coronary artery Electrocardiographic changes typical of those of myocardial injury result from experimental pulmonary emboli, not large enough, however, to cause a significant reduction in the pulmonary blood flow The effect seems to be mediated through the vagus nerve, for in rabbits, according to Radnai and Mosonyi,³⁶ the phenomenon is abolished by bilateral vagotomy The view of McGinn and

32 Wiggers, C J, in Levy, R L Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1937

33 von Bergmann, G Das "epiphrenale Syndrom" Seine Beziehung zur Angina Pectoris und zum Kardiospasmus, Deutsche med Wchnschr 58 605, 1932

34 Scherf, D, and Schonbrunner, E Ueber den pulmocoronaren Reflex bei Lungenembolien, Klin Wchnschr 16 340, 1937

35 Hochrein, M, and Keller, J Untersuchungen am Koranarsystem, Arch f exper Path u Pharmacol 159 300, 1931

36 Radnai, P, and Mosonyi, L Ueber den Gefassverengernden Pulmocoronar-reflex, Ztschr f d ges exper Med 98 651 1936

White³⁷ that these changes are secondary to dilatation of the right side of the heart is not plausible, since this dilatation of itself does not produce the same electrocardiographic pattern. The occurrence clinically and electrocardiographically of a coronary symptom complex in pulmonary embolism in human beings is best explained by the pulmonary-coronary reflex.

3 Reflexes Originating Centrally. Another mode of coronary vasomotor activity is that occurring with central vasomotor stimulation. There are probably a variety of effective stimuli, of which at least one, carbon dioxide acting centrally, produces coronary vasoconstriction.

Extracardiac Reflexes Affecting the Coronary Flow.—We have dealt so far with reflex vasomotor phenomena directly affecting the coronary arteries. The coronary flow is, however, passively altered by reflex phenomena in other organs, notably the liver, spleen and skin, which normally under conditions of increased myocardial oxygen need yield blood to the heart and other organs and may properly be called depot organs. The importance of the depot organs may be fully understood when it is appreciated that 1,500 cc of blood may be locked in the liver by the contraction of the hepatic veins. Sympathetic stimulation, epinephrine and ephedrine dilate the hepatic veins and aid in the surrender of blood from the liver and other depot organs. Histamine, on the other hand, constricts these veins. The peripheral failure from collapse due to doses of histamine is probably in part the result of constriction of the hepatic veins, which further pools the blood in the splanchnic bed. Closure of the veins of the blood depot organs or their failure to open may, according to Lichtwitz,³⁸ produce myocardial anoxia and an anginal syndrome.

Conditions in which the depot organs do not readily surrender blood to increase the venous return cause a relative myocardial insufficiency of oxygen, such a situation is the digestive state, and the frequency of coronary attacks after a heavy meal, especially in association with physical effort, is probably related to this fact. The frequent enlargement of the liver and spleen in anginal attacks is indicative of the role of the depot organs. Cutaneous vasodilatation under conditions of heat may act similarly. Anginal seizures on exposure to cold or after a meal are more understandable on the basis of a disturbed blood supply than on the basis of coronary spasm.

Finally, the condition of the abdominal musculature, by altering the intra-abdominal pressure, also plays a role in maintaining the circulation

37 McGinn, S., and White, P. D. Acute Cor Pulmonale Resulting from Pulmonary Embolism. Its Clinical Recognition, *J. A. M. A.* **104** 1473 (April 27) 1935.

38 Lichtwitz, L. *Pathologie der Funktionen und Regulationen*, Leiden, A. W. Sijthoff's Uitgeversmaatschappij N. V., 1937.

of the heart The emptying of the blood depots is facilitated by a strong abdominal musculature, which aids the venous return from the splanchnic area during descent of the diaphragm

HUMORAL FACTORS

The importance of humoral factors in the coronary circulation has been well demonstrated Of great importance is epinephrine, a powerful constrictor which affects through its peripheral action the sympathetic nervous system The effect of epinephrine on the coronary arteries is debatable, since some observers have reported constriction and others dilatation It has been shown that epinephrine may precipitate anginal seizures and that it predisposes to left ventricular failure³⁹ Whether the effect is due to a direct action on the heart, an elevated blood pressure, tachycardia or a specific action on the coronary arteries cannot be stated

Additional humoral agents are histamine and the vasopressor substance of the posterior lobe of the pituitary gland The predominant action of histamine is a constrictor effect on the arterioles and a dilator effect on capillaries Vasopressin acts directly on smooth muscle, constricts the arterioles and probably constricts the coronary arteries In experimental hypertension, such as that produced by Goldblatt,⁴⁰ a vasopressor substance is considered to be produced by the ischemic kidney The action of this humoral substance on the coronary arteries is not known

Another endogenous agent, acetylcholine, produces marked arteriolar and capillary dilatation In the coronary arteries, however, the experimental evidence suggests that acetylcholine causes coronary constriction Hall, Ettinger and Banting⁴¹ produced experimental coronary thrombosis and myocardial damage in dogs by prolonged injection of dilute solutions of acetylcholine In older animals, changes in the arterial wall, thrombosis and myocardial infarction were encountered, while in young dogs myocardial damage occurred without coronary thrombosis By stimulation of the vagus nerve alone they produced diffuse myocardial degeneration, small infarcts and subendocardial hemorrhages, together with electrocardiographic changes Vagal stimulation in dogs to which physostigmine had been given resulted in more extensive cardiac lesions These experiments indicated the development of organic disease solely from humoral stimulation

39 Smith, F M, in Levy, R L Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1937

40 Goldblatt, H, Lynch, J, Hanzal, R F, and Summerville, W W Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J Exper Med* **59** 347, 1934

41 Hall, G E, Ettinger, G H, and Banting, F G An Experimental Production of Coronary Thrombosis and Myocardial Failure, *Canad M A J* **34** 9 1936

OTHER FACTORS

The concept of temporary functional disturbance in angina pectoris is supported by clinical as well as by experimental transitory anginal seizures. Such transitory seizures are sometimes accompanied by temporary electrocardiographic changes. Brow and Holman,⁴² Feil and Siegal⁴³ and Wood and Wolferth,⁴⁴ by experimental transient coronary constriction, demonstrated alterations of the terminal deflections of the electrocardiogram, which returned to normal when adequate oxygenation was restored. These observers, as well as Parkinson and Bedford⁴⁵ and Hall,⁴⁶ reported electrocardiographic changes in patients with transitory anginal seizures simulating those of the early stages of cardiac infarction. They concluded that changes in the ST portion of the electrocardiograms of patients with angina pectoris represent transient vascular changes in the heart. The electrocardiographic changes in experimental cardiac ischemia may appear and disappear within two minutes, a period comparable to that of an anginal attack in a human being. If in the experimental animal, however, the clamp on the coronary artery is left on long enough, cardiac infarction results which is similar to that in man with acute coronary thrombosis.

Transient anginal pain and cardiac infarction affect the electrocardiogram similarly. Since paroxysmal pain cannot be explained solely in terms of morbid anatomy, which is frequently the same as before, during and after the anginal seizure, it seems reasonable to regard the anginal attack even in many patients with organic coronary involvement as due to a transient disturbance of function. The mechanisms underlying both the electrocardiographic changes and the pain are probably the same whether the anoxemia is short and produces reversible myocardial change or is prolonged and results in permanent myocardial damage.

In the brain, which is functionally similar to the heart in many ways, it has also been shown that functional factors may play a significant role

42 Brow, G. B., and Holman, D. V. Electrocardiographic Study During a Paroxysm of Angina Pectoris, *Am Heart J* **9** 259, 1933.

43 Feil, H., and Siegal, M. L. Electrocardiographic Changes During Attacks of Angina Pectoris, *Am J M Sc* **175** 255, 1928.

44 Wood, F. C., and Wolferth, C. C. Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, *Arch Int Med* **47** 339 (March) 1931.

45 Parkinson, J., and Bedford, D. E. Electrocardiographic Changes During Brief Attacks of Angina Pectoris, *Lancet* **1** 15, 1931.

46 Hall, D. Electrocardiograms of Two Patients During Attacks of Angina Pectoris, *Lancet* **1** 1255, 1932.

in producing organic disease Spielmeyer⁴⁷ has shown that functional spasm of the cerebral vessels may cause an impairment of nutrition resulting in degeneration of the central nervous system After epileptic seizures he observed fresh changes in the brain which he thought due to temporary circulatory impairment His colleague Neuburger⁴⁸ found recent destruction of cardiac muscle after epileptic seizures

A variety of physiologic mechanisms, derangements of which may lead to myocardial anoxia or even infarction, have been discussed Many of these, more specifically those which do not directly involve localized vascular areas, have a generalized effect on the heart Profound disturbances of these, it would be expected, would lead to generalized pathologic changes in the myocardium rather than to localized infarcts, such as existed in our cases This objection is minimized by certain considerations First, while the disturbance may be generalized, the most severe and irreversible pathologic changes would occur in the areas of greatest functional stress The end result might therefore appear as a localized lesion Secondly, experimental evidence supports this concept In the experiments on orthostatic collapse produced by maintaining a guinea pig in the vertical position, the myocardial anoxia is undoubtedly generalized Nevertheless, the lesions are preponderant in certain areas Other experiments, like the injections of acetylcholine previously mentioned, also produce preponderantly localized lesions

Finally, it is conceivable that certain local factors in the myocardium may produce specific effects on associated vessels and thus intensify the disturbance in a given area With myocardial anoxia there is a local increase in carbon dioxide, lactic acid, phosphoric acid and other metabolites, with a lowering of the p_H These factors as well as oxygen lack per se tend to dilate the coronary arteries However, with the increase in vascular permeability and the alteration of chemical equilibrium due to ischemia, edema results which affects the walls of the vessels themselves as well as the myocardium

As far back as 1912, Klemensiewicz,⁴⁹ who studied the relation of edema to ischemia, stated that in the course of ischemia changes in permeability may occur in the vascular wall leading to localized edema of the wall which may go on to irreversible organic lesions Thrombosis, if it occurs after such changes in the wall, may be the result rather than

47 Spielmeyer, W Influence of Functional Circulatory Disturbances on the Central Nervous System, *J Nerv & Ment Dis* **71** 293, 1930

48 Neuburger, K Herz, Epilepsie, Angina pectoris, *Klin Wchnschr* **12** 1355, 1933

49 Klemensiewicz, R Die Pathologie der Lymphströmung, in Krehl, L., and Marchand, F Handbuch der allgemeinen Pathologie, Leipzig, S Hirzel, 1912, vol 2, p 341

the cause of myocardial ischemia. It seems reasonable to postulate that if the edema of the vascular wall is of sufficient severity to produce necrosis of the myocardium but not to produce irreversible changes in the vessel, subsequent examination may show destruction of the cardiac muscle without corresponding damage to the vascular wall.

It follows that there is no strict separation between the cases in which there is a functional disturbance and those in which there is organic thrombosis. A physiologic approach to the problem provides a more satisfactory interpretation of the wide diversity of clinical and anatomic features in cases ranging from those of purely functional disorders to those of advanced organic coronary disease.

SUMMARY AND CONCLUSIONS

Fifteen cases of myocardial infarction without demonstrable occlusion of the coronary arteries were studied. Arteriosclerosis of the coronary arteries was minimal. In 1 case all the major vessels were sectioned serially.

A variety of physiologic mechanisms which might account for myocardial damage in the absence of vascular occlusion is outlined. These may be mechanical, reflex or humoral. 1. Mechanical factors include temporary falls in intra-aortic blood pressure, tachycardia, phasic variations of the coronary flow and cardiac hypertrophy. Changes in either the number of formed elements or the viscosity of the blood, such as are seen in anemia and polycythemia, are contributory factors. 2. Reflex factors may produce anoxia of the myocardium from failure of adequate compensatory dilatation of the coronary arteries or from coronary constriction. The stimuli for these reflexes may arise either in the heart and its associated structures or in other parts of the body. 3. Humoral factors and possibly other agents, including acetylcholine, epinephrine and vasopressin, also alter the caliber of the coronary arteries.

The presence of hypertension in 13 of our 15 cases is of great interest. Vasoconstrictor phenomena are common in hypertension, and it is conceivable that extreme coronary vasoconstriction may have played a role.

The underlying cause of the anginal seizure, whether transitory or associated with myocardial infarction, is ischemia of the myocardium. Similarly, the electrocardiographic changes in both instances are also the result of myocardial ischemia. The duration of ischemia will determine whether the cardiographic and myocardial changes are reversible or not.

Though the occurrence of the type of case reported by us is infrequent, it is nevertheless of importance, since similar physiologic factors must also play a role in many cases of ordinary coronary disease and myocardial damage.

HEMOLYTIC JAUNDICE

IMMEDIATE AND DELAYED CHANGES IN THE BLOOD AFTER SPLENECTOMY

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AND

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OMAHA

That splenectomy causes a "clinical cure" of hemolytic jaundice has been well known for some time, but only recently has our attention been called to the immediacy of the changes in the blood that follow the operation¹ In the past four years 26 cases of typical familial hemolytic jaundice have been observed,² in 12 of which the spleen was removed without fatality Eight of the splenectomized patients have been subjected to careful detailed study with special reference to changes occurring in the blood during and immediately after splenectomy It is our purpose to present the results of this study together with control observations on 5 additional cases of "refractory" anemia in which splenectomy was performed We hope that our additional information concerning the action of the spleen will be of some clinical value to the physician in his understanding and handling of the patient with hemolytic jaundice

METHODS

In this group of 8 cases, the diagnosis of hemolytic jaundice was made without question from the detailed individual history and family history, a careful physical examination and complete and thorough hematologic studies, which included blood counts, hematocrit studies, erythrocytic fragility tests, reticulocyte counts and determinations of the icterus indexes and van den Bergh reactions The period of control observation before splenectomy varied in different instances from a few

From the Department of Medicine and the Department of Surgery, the University of Nebraska College of Medicine

1 Doan, C A , Wiseman, B K , and Erf, L A Studies in Hemolytic Jaundice, Ohio State M J **30** 493-504 (Aug) 1934 Doan, C A , Curtis, G M , and Wiseman, B K The Hematolytopoietic Equilibrium and Emergency Splenectomy, J A M A **105** 1567-1575 (Nov 16) 1935 Curtis, G M , Doan, C A , and Wiseman, B K Splenectomy for Hemolytic Crises, Ann Surg **104** 892-903 (Nov) 1936

2 Sharpe, J C Hemolytic Jaundice, Internat Clin **2** 146-167 (June) 1937

weeks to many months. Additional laboratory and roentgen studies were made, but the results are not important in the consideration of this particular problem. The patients were all white. There were 7 females and 1 male. Their ages varied from 4 to 42 years.

The patients were hospitalized several days prior to operation, and complete studies of the blood were made daily. On the day of operation certain studies³ were made before the anesthetic was administered, during surgical manipulation of the spleen but before ligation of its pedicle and at fifteen minute periods thereafter during the remainder of the operation. The samples of blood were obtained from a stab puncture of the finger tip. These same studies were carried out two, four, eight, twelve, twenty-four and forty-eight hours after operation and every three to five days thereafter during hospitalization. Routine checks of the blood counts were made at varying intervals every one to three months after splenectomy.

The operations were purposely performed with various types of anesthesia, including spinal anesthesia and anesthesia induced with cyclopropane, nitrogen monoxide and ether, and avertin with amylene hydrate and ether. For the most part the surgical approach and technic of Wilkie⁴ were used. In this group, neither transfusions nor any other type of antianemic therapy was given either preoperatively or postoperatively, so that any change in the blood picture was considered directly attributable to the splenectomy.

With the same plan of study, a group of control observations were made on 5 patients with severe refractory anemia before, during and after splenectomy. The patient in case 1 was a woman 21 years of age, the remaining patients were older, 2 men and 2 women whose ages varied from 52 to 64 years. All had marked and persistent anemia, acholuric jaundice, reticulocytosis, hyperplasia of the bone marrow and gross splenomegaly for which, even after complete postmortem examinations in 3 of the 5 cases, the cause could not be clearly established. Splenectomy was tried only after a long period of observation in which all forms of medical therapy to combat the anemia had failed. These patients differed from those with typical hemolytic jaundice in that there was no evidence of a familial tendency, the blood picture was characterized by an absence of spherocytosis, and the fragility, though slightly altered, was not definitely increased. The patient in case 4 died on the third postoperative day, of thrombosis of the splenic vein,⁵ the patient in case 2 died of postoperative pneumonia one week after splenectomy, the patient in case 3 died as the result of postoperative hemorrhage following a subsequent cholecystectomy nine months after splenectomy. The patients in cases 1 and 5 were living twelve and seven months after splenectomy, but in neither case had the clinical or the hematologic picture changed from that observed prior to operation. At a later date this group of cases of atypical hemolytic anemia, recently referred to by Thompson,⁶ will serve as the basis of a detailed report on the controversial question of the "acquired" or refractory type of hemolytic anemia.

3 Erythrocyte, leukocyte, differential and reticulocyte counts and determinations of the icterus index and the hemoglobin content of the blood.

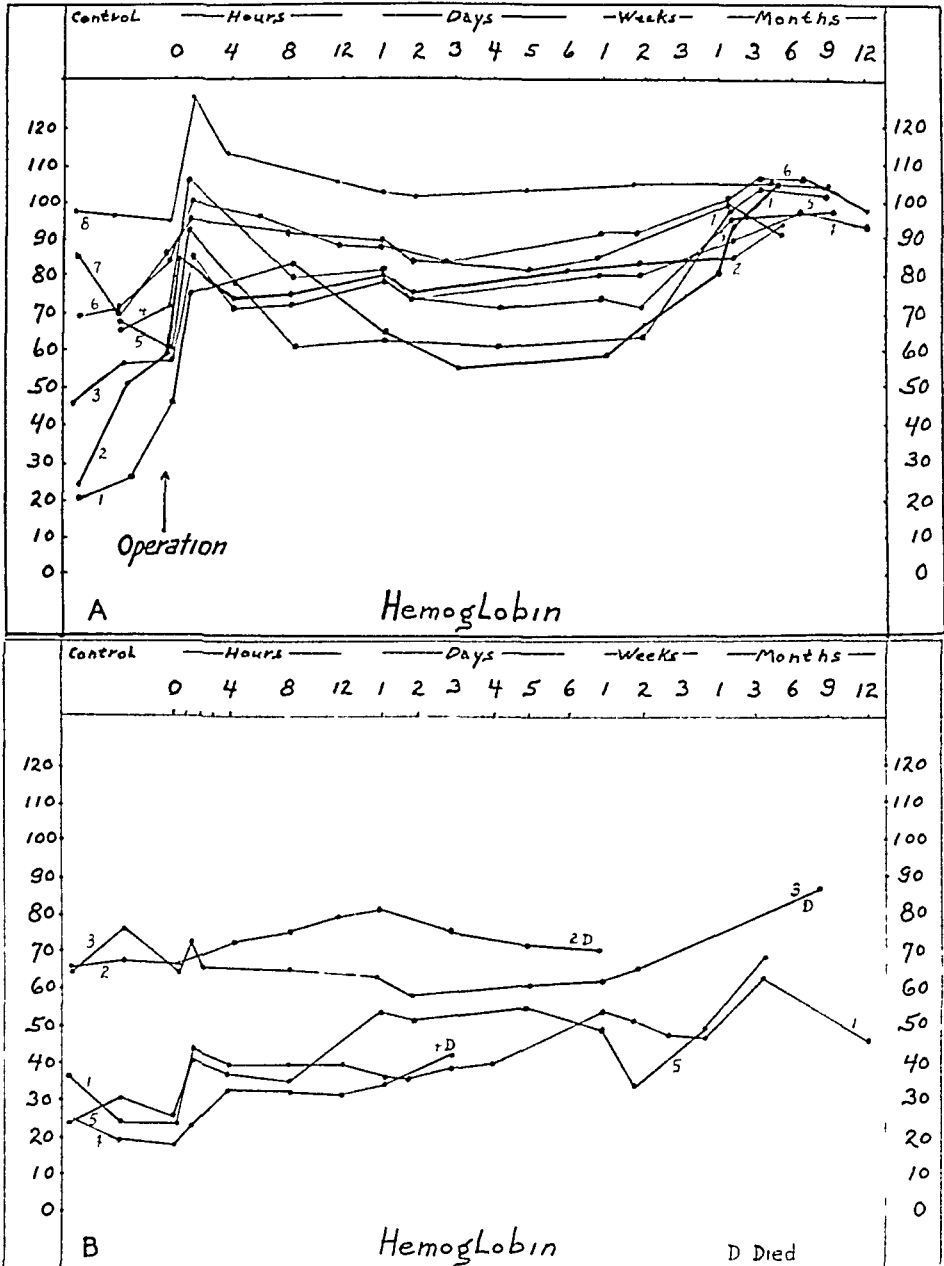
4 Wilkie, D. P. D. Splenectomy. Its Indications and Technique, *Am J Surg* **14** 340-355 (Oct) 1931.

5 Davis, H. H., and Sharpe, J. C. Splenic Vein Thrombosis Following Splenectomy, *Surg, Gynec & Obst* **41** 678-682 (Nov) 1938.

6 Thompson, W. P. Hemolytic Jaundice. Diagnosis, Behavior and Treatment, *J A M A* **107** 1776-1781 (Nov 28) 1936.

RESULTS

Hemoglobin—In the group of 8 cases of typical hemolytic jaundice, the value for hemoglobin at the time of operation in 5 cases was 70 per cent or below, while in the other 3 cases it ranged from 82 to 96 per cent



(chart 1 A) From the time the anesthetic was given to the point of ligation and cutting of the splenic pedicle there was a necessary ten to twenty minute interval of handling, manipulating and squeezing the spleen during the process of freeing the organ from adhesions and its normal ligamentous attachments. During this period, in each of the 5

cases of severe anemia there was a sharp rise in the hemoglobin content of the blood, varying from 16 to 32 per cent. There was no appreciable change, however, in cases 6, 7 and 8, in which the control hemoglobin determinations were within normal limits. After the splenic pedicle was ligated and the spleen removed, the hemoglobin continued to increase slightly (3 to 12 per cent) during the first postoperative hour in the first 5 cases and more sharply (10 to 28 per cent) in the remaining 3 cases. In other words, at the end of the first hour after splenectomy the hemoglobin had increased in every case from 10 to 35 per cent, with the astounding average of 23.2 per cent for the group. From our observations, it would seem that the lower the preoperative hemoglobin level, the more rapid and more marked the increase, the change occurring, for the most part, during actual surgical manipulation of the spleen. There seemed to be no direct relation, however, between the size of the spleen and the degree of change occurring in the blood during its removal.

After the sudden increase of hemoglobin during the operation and the first hour after the operation, there was a slow but definite drop during the first eight hour period, the decrease varying from 3 to 33 per cent and averaging 16 per cent for the group. The decrease in hemoglobin continued in most cases to about the third postoperative day, and though it approached, in no instance did it actually return to, the preoperative level. During the remainder of the first week after removal of the spleen, although the chart shows a definite "leveling off" with little or no change in the amount of hemoglobin, the patient showed a daily clinical improvement associated with a rapid return to normal of the reticulocyte count and the icterus index. The value for hemoglobin each week thereafter showed a slow but sustained improvement, returning to normal limits by the end of four to eight weeks.

The control series of 5 splenectomized patients with atypical hemolytic anemia showed no such temporary immediate or permanent secondary change in hemoglobin as was uniformly observed in cases of familial hemolytic jaundice (chart 1 *B*). In the 3 cases of this group in which anemia was most severe, manipulation of the spleen during operation caused a rise of 6 to 14 per cent in the first hour, but it in no way compared to that observed in cases of familial hemolytic jaundice. In addition, the subsequent postoperative curve did not show the gradual increase to normal. The 3 patients who survived the first postoperative month showed an average of 57 per cent for the group as compared to their preoperative average of 42 per cent. At the time of writing the 2 remaining living patients, twelve and seven months after removal of the spleen, remain only slightly improved.

Erythrocytes—At the time of operation, the control red blood cell counts of 7 of the 8 patients with typical familial hemolytic jaundice

were below 4,000,000 per cubic millimeter. Three of them were between 2,000,000 and 3,000,000 cells per cubic millimeter (chart 2 A). In case 8 the erythrocyte count was 4,600,000 on the day of splenectomy. Again,

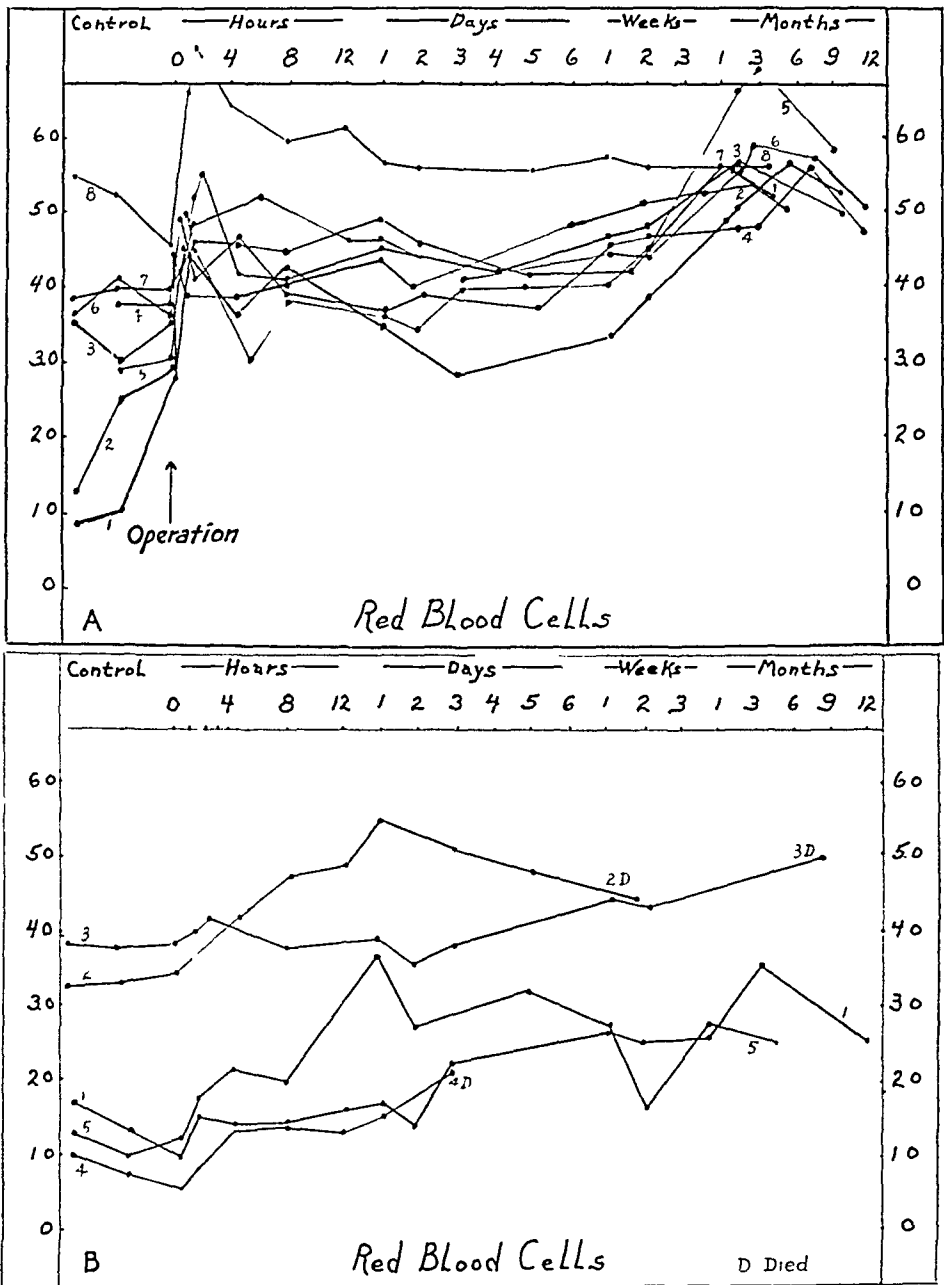


Chart 2—A, hemolytic jaundice, B, atypical hemolytic anemia

irrespective of the red blood cell level at the time operation started, a dramatic response was observed during the short interval of handling the spleen before actual ligation of the pedicle. In this fifteen to twenty minute interval, the increase varied from 200,000 to 1,900,000 cells, the average for the group being 980,000. As observed in the hemoglobin

determinations, the increase of red cells continued, though not as sharply, for one to two hours after the spleen had been removed. Up to this time the average increase for the group from the initial preoperative count was 1,100,000 cells. After the second hour the curve for the group varied somewhat, the count in 4 cases showing a sharp decline, that in 2 continuing to increase slightly for a few more hours and then beginning its descent and that in the remaining 2 "leveling off" for six to twelve hours before showing a decrease. All, however, within the first forty-eight hour period gradually fell to approach their preoperative control determinations.

Though there was some individual fluctuation on the curves during the first week after operation, the trend for the group showed a beginning upward swing that carried each count to approximately 5,000,000 cells by the end of the first month. The patient in case 3 had temporary polycythemia, the erythrocyte count being 7,200,000 three months after operation.

In the group of cases of atypical hemolytic anemia (chart 2 *B*) a definite pattern of response to splenectomy was again lacking. No sharp immediate increase of any degree was observed during the operative interval. Although in cases 2 and 5 there were striking increases at the end of twenty-four hours, the counts in both promptly declined to and remained at subnormal levels by the end of the first week. The patients in cases 1 and 5, twelve and seven months respectively after splenectomy, were still moderately anemic.

Leukocytes—In each case of hemolytic jaundice, splenectomy caused a profound change in the number of leukocytes (chart 3 *A*). Before operation the average white cell count for the group was 11,800 per cubic millimeter. After the manipulative phase and before ligation of the splenic vessels, the number of white cells began a steep and rapid ascent. The increase varied from 2,600 to 48,000 cells, the average for the group being 28,300 cells. The rise in the leukocyte count continued during and after the operation, reaching a maximum height in from one to eight hours postoperatively and ranging from 14,000 to 51,250, with an average of 45,800 for the group. The increase was uniformly of the polymorphonuclear series, chiefly the younger forms, the total percentage varying from 89 to 97 at the peak of the increase.

After this rapid initial rise in the leukocyte count there was a slower decrease for the first week after splenectomy, approaching but not returning to the normal levels. This postoperative leukocytosis, with a leukocyte count ranging from 10,000 to 16,000 cells and a normal differential formula, has persisted in each case up to the time of writing.

In the cases of atypical hemolytic anemia (chart 3 *B*), with the exception of case 3, the amazing sudden increase in leukocytes did not

occur during the operation With a much lower preoperative leukocyte count than was observed in the first group, averaging 3,640 cells per cubic millimeter, splenectomy produced only a slight increase in the

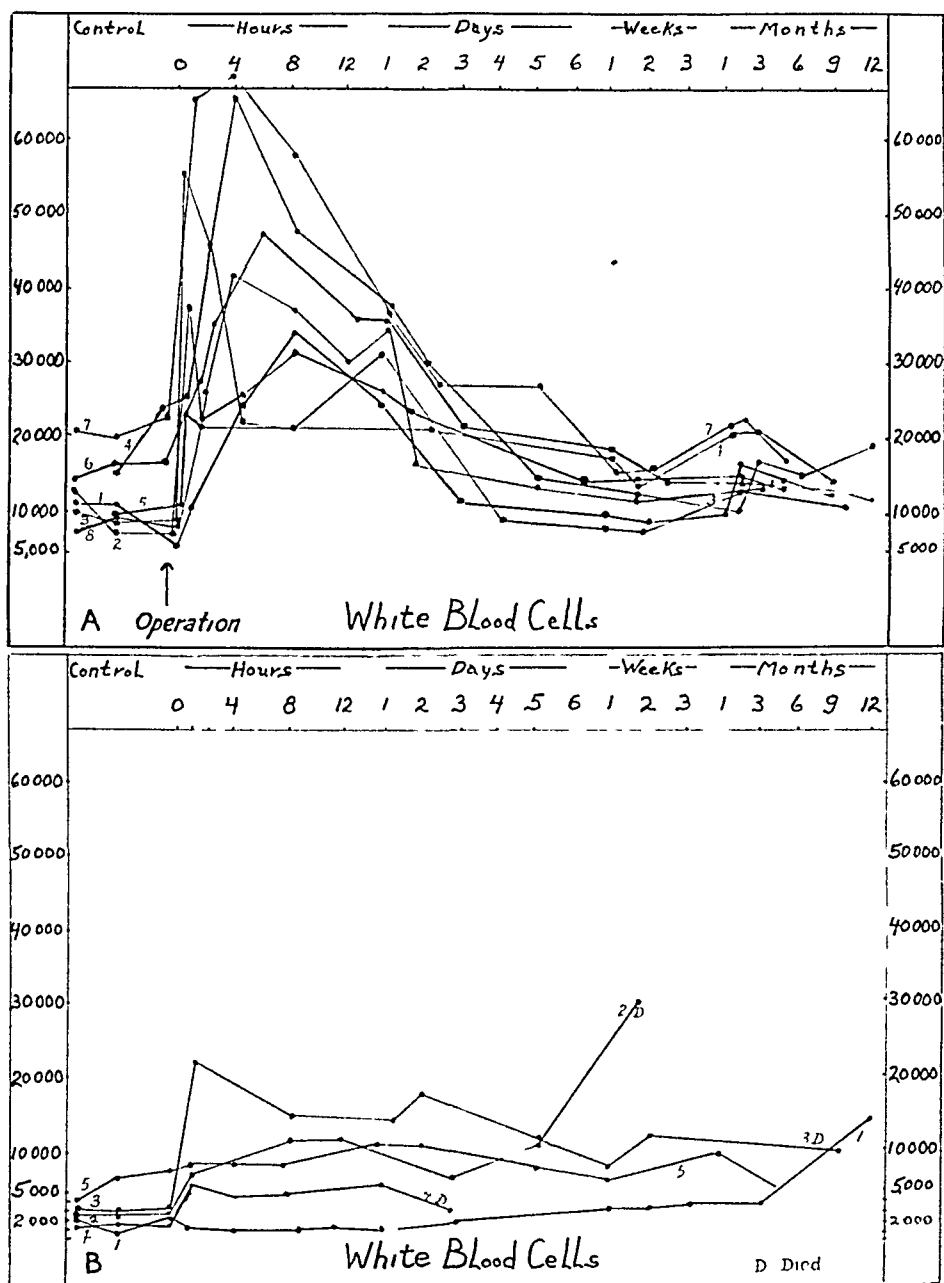


Chart 3—A, hemolytic jaundice, B, atypical hemolytic anemia

number of cells Except for a leukocyte count of 32,000 observed in case 2, in which the patient succumbed to postoperative pneumonia, the average for the group at the end of the first week after splenectomy was 4,700 white cells per cubic millimeter

COMMENT

From these observations on the changes occurring in the blood during and after removal of the spleen, two problems naturally present themselves 1 What are the factors responsible for the production of these unusual changes? 2 Of what clinical use and importance are these changes in considering the patient with hemolytic jaundice?

At present there is almost universal agreement among clinicians that gradual improvement in the red cell level follows splenectomy for hemolytic jaundice.⁷ The striking suddenness with which such changes occur was pointed out first by Glover and Fargo⁸ and later by Doan and his associates.¹ The latter group found in addition that after splenectomy a major increase, frequently of 1,000,000 or more red cells per cubic millimeter, occurred immediately, before the patient left the operating table. They further stated that studies of the blood volume proved this erythema to be not simply a relative cellular increase dependent on some loss in plasma volume but an immediate, large and significant increase in the actual circulating erythrocytic cell volume. They concluded

The disgorgement of the sequestered blood cells from the splenic reservoir incident to operation, and the sudden elimination of the destructive activity of the splenic phagocytes render more effective the unusually active erythropoiesis and erythrocytic delivery that characterize the bone marrow in hemolytic anemia.

Before attempting to explain the results of our observations, it would first be pertinent to review briefly a few of the more recently discovered and important facts concerning the fundamental physiologic action of the spleen. Barcroft⁹ has definitely shown experimentally that the spleen acts as a reservoir of red blood corpuscles and that under various influences it is capable of marked alterations in its volume, with resulting changes in the numbers of blood cells in the peripheral circulation. Cruickshank¹⁰ estimated the amount of blood expelled from the spleen by a single contraction to be from 26 to 56 per cent of the total blood volume of the animal. Miller and Rhoads,¹¹ in a

7 Cheney, W. F., and Cheney, G. Chronic Hereditary Hemolytic Jaundice, *Am J M Sc* **187** 191-212 (Feb.) 1934. Pemberton, J. D. Results of Splenectomy in Splenic Anemia, Hemolytic Jaundice, and Hemorrhagic Purpura, *Ann Surg* **94** 755-765 (Oct.) 1931.

8 Glover, D. M., and Fargo, W. C. Familial Hemolytic Jaundice, *Ohio State M J* **29** 428-432 (July) 1933.

9 Barcroft, J. Alterations in the Volume of the Normal Spleen and Their Significance, *Am J M Sc* **179** 1-30 (Jan.) 1930.

10 Cruickshank, E. W. H. Output of Hemoglobin and Blood by the Spleen, *J Physiol* **61** 455-464 (June) 1926.

11 Miller, D. K., and Rhoads, C. P. The Effect of Splenic Contractions on the Formed Elements of the Blood in a Case of Anemia and Splenomegaly, *J Clin Investigation* **12** 1009-1033 (Nov.) 1933.

study of the spleen as a reservoir of blood, reported a case of anemia and splenomegaly in which it was possible to induce marked contraction of the spleen by the parenteral use of various drugs. Accompanying the induced splenic contractions, there occurred within a few minutes marked increases in the number of cellular elements of the circulating blood, amounting to as much as 520,000 red blood cells per cubic millimeter and 15 per cent hemoglobin. Determinations of blood volume after contraction of the spleen showed a slight increase in the total blood volume and a slight reduction of the plasma volume.

From these observations, there seems to be little doubt concerning the capacity of the spleen to act as a storehouse for blood elements and by altering its volume to cause striking changes in the peripheral blood stream. Some of these changes in the blood, however, have been induced in patients without spleens. Patek and Doland¹² made studies of the blood before and after the subcutaneous injection of epinephrine hydrochloride in normal subjects, patients with hemolytic jaundice before and after splenectomy and patients with splenomegaly from miscellaneous diseases. In no case was there any significant change of concentration of red blood cells, in the hematocrit reading or in the hemoglobin. In all cases leukocytosis involving the mature forms of both myeloid and lymphoid cells occurred. Since the changes were not greater in patients with spleens than in splenectomized patients they appeared to be due not to splenic contractions but to a mechanical alteration in the blood stream. Using epinephrine hydrochloride, we had independently made the same observations and come to the same conclusions in a few selected cases both before and after splenectomy.

In order to evaluate any alteration in the blood during and after splenectomy, one must first know what changes, if any, take place during any major operative procedure done under various types of preoperative medication and anesthetics. This problem has been adequately covered by former investigators¹³ who, working with a large series of surgical patients whose illness was not complicated by infection or hemorrhage, came to the following conclusions: 1. Slight change or no change in the hemoglobin or red blood cells occurs during or after various operations performed with the aid of local, inhalation or

12 Patek, A. J., and Doland, G. A. The Effect of Adrenalin Injections on the Blood of Patients With and Without Spleens, *Am J M Sc* **190** 14-21 (July) 1935

13 Mann, F. C. Some Bodily Changes During Anesthetics, *J A M A* **97** 172-175 (July 15) 1916. Meleney, F. L. A Study of Anteoperative and Postoperative Blood Counts in Non-Infectious Surgical Conditions, *Ann Surg* **67** 129-148 (Feb.) 1918. Witter, M. S. Postoperative Leucocytosis, *Surg, Gynec & Obst* **40** 23-30 (Jan.) 1925. Taylor, I. B., and Water, R. M. Leucocytosis Following Inhalation Anesthesia, *Anesth & Analg* **14** 276-281 (Nov-Dec.) 1935

spinal anesthetics 2 Leukocytosis occurs, the leukocyte count being two to three times the preoperative count, reaching its peak in four to eight hours and returning to normal numbers at the end of four to five days, with a slight lag of a day or so in the return of the differential formula Inhalation anesthetics cause a higher increase in the leukocyte count than do anesthetics administered by the spinal route The increase appears to be due to direct stimulation of the bone marrow and not related to the spleen We have confirmed these observations on a relatively small number of surgical patients

The changes in the cellular elements of the blood which occur after transfusion have been studied by Sibley and Lundy¹⁴ These authors have shown that after a transfusion of 500 cc of citrated blood, an increase of the value for hemoglobin of from 12.7 to 16.8 per cent (21.2 to 28 Gm per hundred cubic centimeters) can be expected at the end of the second day in those cases in which reactions do not occur and in which bleeding does not follow the transfusion

With this background it seemed logical for us to use as controls patients with conditions closely allied to hemolytic jaundice, for whom splenectomy was tried as a therapeutic measure This is especially important when one considers the factor of squeezing and manipulation of the spleen and the question of an autotransfusion effect that would necessarily be absent during any other type of operation

Turning then to our observations on the group of cases of typical hemolytic jaundice, we may corroborate the conclusion of Doan and his associates¹ that an immediate and dramatic change in the cellular elements of the blood occurs during splenectomy We have been able to demonstrate, however, that this change is temporary, lasting only a few hours, and it appears to be merely the result of an outpouring of blood cells into the peripheral circulation from an enlarged splenic reservoir that is squeezed and handled during the surgical procedure In each instance the reduction of splenic size and volume that occurs during operation is visible and obvious

After splenectomy there is a readjustment of the fluid balance, and the hemoconcentration decreases within forty-eight hours, with subsequent reduction in the number of cells to almost the preoperative level With removal of the spleen and its destructive effect on the erythropoietic equilibrium, the hyperplastic bone marrow, so characteristic of this specific disease entity, quickly compensates for the reduced numbers of cells and a second and more gradual but permanent increase, this time to normal limits, takes place This secondary rise in the hemoglobin level and the erythrocyte count appears similar to that seen after

14 Sibley, W. L., and Lundy, J. S. The Behavior of the Hemoglobin After Blood Transfusion, *Surg., Gynec. & Obst.* **67**: 293-295 (Sept.) 1938

the reticulocyte shower in pernicious anemia during adequate liver therapy. Three of these original patients have undergone a later cholecystectomy, during which there was no appreciable change in the amount of hemoglobin or the number of erythrocytes, although a moderate but transitory increase in the leukocyte count occurred.

An interesting feature of our observations was the gross difference between the changes in the blood in our cases of typical hemolytic jaundice and those in our cases of so-called atypical hemolytic anemia. If, as we have assumed, the initial changes that occurred in the former group were merely an autotransfusion effect of squeezing an enlarged spleen before its removal, the same dramatic increase should have resulted during splenectomy in the latter group. This, however, was not the case. A possible explanation for this interesting contrast lies in the differences in the histologic appearance of the spleen. In the patients with hemolytic jaundice the spleen was essentially normal histologically, though there was considerable congestion of the splenic pulp. On the other hand, in the second group the sections of the spleen showed little, if any, congestion but frequently showed mild fibrosis and reticular cell hyperplasia with a fairly large number of free histiocytes and nucleated red blood cells. Such a distinct difference in the splenic histologic picture may account for the respective reactions of the elements of the peripheral blood occurring during and after splenectomy. Furthermore, it would seem obvious that splenectomy in cases of refractory anemia has no beneficial effect on the anemia. This problem, together with the peculiar histiocytic reaction observed in the spleens in such cases, will serve as the basis of a future report.

As a result of our experience with the promptness of the changes occurring in the blood during and after splenectomy, we have not hesitated to suggest splenectomy for patients with hemolytic jaundice even in the presence of moderate or severe anemia. In our series of 12 splenectomized patients the results have been uniformly excellent. It is our practice to recommend splenectomy for patients with clinical manifestations of the disease, irrespective of age and independent of the severity of involvement and the presence of complications. In such patients the chronicity of symptoms and the risk of serious complications more than offset the low risk of operation. Although we have had several of our patients under observation during typical hemolytic crises, we have not yet felt it necessary to resort to splenectomy as an "emergency" procedure as advocated by Doan and his associates¹ and therefore have not had the opportunity to observe the response of this type of patient. It would seem, however, that if, with this type of critically ill patient, the first increase of blood occurring during splenectomy were followed by several daily blood transfusions, the subsequent

decrease could be averted to a large degree and the danger of post-operative complications greatly lessened

SUMMARY

In patients with familial hemolytic jaundice, splenectomy caused dramatic, immediate changes in the blood, which persisted for only a few hours. These primary changes were the result of an autotransfusion effect from surgical manipulation of the enlarged splenic reservoir.

During the first four to six weeks after splenectomy, a second rise, gradual and permanent, to normal limits was observed in the hemoglobin content and the erythrocyte count. This second increase resulted from removal of the destructive function of the spleen, which previously kept these values below normal in spite of a hyperplastic bone marrow.

No comparable blood changes were observed during or after splenectomy in a group of cases of atypical hemolytic anemia, in various general abdominal operations or in splenectomized patients with familial hemolytic jaundice undergoing cholecystectomy.

POLYOSTOTIC FIBROUS DYSPLASIA

REPORT OF A CASE

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AND

ABRAHAM CANTAROW, M D

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The skeletal disease known as polyostotic fibrous dysplasia has been described in the literature under a variety of designations, including osteodystrophia fibrosa unilateralis, osteitis fibrosa localisata, osteodystrophia fibrosa cystica generalisata, fibrous osteodystrophy and osteitis fibrosa disseminata. Since the osseous changes, which in this condition are usually predominantly or exclusively unilateral, simulate roentgenographically those due to hyperparathyroidism (osteitis fibrosa cystica, Recklinghausen's disease of bone), it is essential to exclude the latter disease so that the patient may not be subjected to unnecessary exploration of the neck and thorax. The term "polyostotic fibrous dysplasia" was applied to this condition by Lichtenstein¹ and Jaffe,² each of whom described a rather characteristic histologic picture of the bone lesion. The present case is reported because it illustrates certain points of importance in differential diagnosis and because we feel that the possible presence of this disorder is frequently overlooked in cases in which the roentgenographic picture of osteitis fibrosa cystica generalisata is present without definite evidence of hyperparathyroidism.

REPORT OF CASE

H. M., a Polish woman aged 20, was admitted to the Jefferson Medical College Hospital in November 1937, complaining of pain in the regions of the hips and increasing deformity of the thighs of nine years' duration. The latter condition had recurred on the right side despite a corrective osteotomy of the femur performed two years previously at another hospital. On a second admission, in April 1938, the patient complained of diffuse pain in the upper extremities and

From the Departments of Orthopedic Surgery and Medicine, Jefferson Medical College Hospital

1 Lichtenstein, L. Polyostotic Fibrous Dysplasia, Arch Surg **36** 874 (May) 1938

2 Jaffe, H. L., in discussion on Garlock, J. H. The Differential Diagnosis of Hyperparathyroidism, with Special Reference to Polyostotic Fibrous Dysplasia (Lichtenstein-Jaffe), Ann Surg **108** 347 (Sept.) 1938

such severe discomfort and weakness in the lower extremities that she had become bedridden. Her family history and past medical history had no bearing on the present illness.

Physical Examination—There was marked bowing of the thighs, especially the right, associated with $\frac{1}{2}$ inch (1.3 cm) shortening of the right lower extremity as compared with the left. There was restriction of motion of both hip joints, due to coxa vara deformities, and considerable tenderness on palpation of the deep tissues of both thighs. Investigation of the genitourinary system and the central nervous system, including studies of the spinal fluid and examination of the eye-grounds and visual fields, revealed no abnormality. The lungs, heart and abdomen appeared normal, and there was no evidence of parathyroid tumor.

Röntgen Examination—The bones of the skull, thorax and spine and both upper extremities appeared normal.

Pelvis—there were many circular radiolucent areas, varying from the size of a pea to that of a walnut, throughout both iliums and most marked just above the acetabulums, especially on the right side. There were osteoporosis and cortical expansion in the rami of the right ischium and the pubis.

Femurs—Coxa vara and outward bowing deformities were present on both sides, more marked on the right, where there was shortening of the entire bone. There was diffuse osteoporosis with cortical thinning throughout the entire shaft. There was considerable expansion of the upper halves of both femurs. Coarse trabeculations simulated cyst formation. A transverse area of increased density below the right lesser trochanter marked the site of the previous osteotomy.

Tibias and Fibulas—There was diffuse osteoporosis with cortical thinning and expansion throughout the right tibia and the left fibula.

Bones of Feet—A large oval radiolucent area was present in the right os calcis, the right scaphoid and cuneiform bones showed diffuse mottling. There was a fusiform expansion of the shafts of the right fourth and fifth metatarsal bones and broadening of the proximal phalanges of the right fourth and the left second toe (fig. 1).

Laboratory Studies—*Blood Count*—Repeated examinations between Nov. 29, 1937 and Sept. 25, 1938 showed hemoglobin ranging from 64 to 96 per cent (Dare), red blood cells from 3,600,000 to 4,850,000 and white blood cells from 6,700 to 11,400. The differential leukocyte count was normal.

Urinalysis—The patient was catheterized and the voided specimens were consistently normal. A twenty-four hour specimen failed to reveal Bence Jones protein.

Calcium and Phosphorus Studies—The following values were recorded:

Date	Serum Calcium, Mg per 100 Cc	Serum Phosphorus, Mg per 100 Cc	Serum Protein, Mg per 100 Cc	Serum Phosphatase Activity, Bodansky Units
Nov. 16, 1937	8.63	3.2		8.5
Nov. 29, 1937			6.4	
Dec. 3, 1937				10.0
April 28, 1938	11.20	2.2		
May 20, 1938	8.43	2.4		6.5
May 27, 1938	9.48	2.1		7.8
June 19, 1938			5.94	
June 27, 1938	8.78	5.2	6.28	11.2
Sept. 7, 1938	11.0	3.2	7.84	2.7

Urinary excretion of calcium and phosphorus for three day periods with a low calcium diet (0.111 Gm of calcium and 0.78 Gm of phosphorus daily) was as follows

Date	Calcium, Mg	Phosphorus, Mg
May 30 June 2, 1937	348	884
June 24 27, 1938	172	2,720
Sept 4 7, 1938	232	1,523

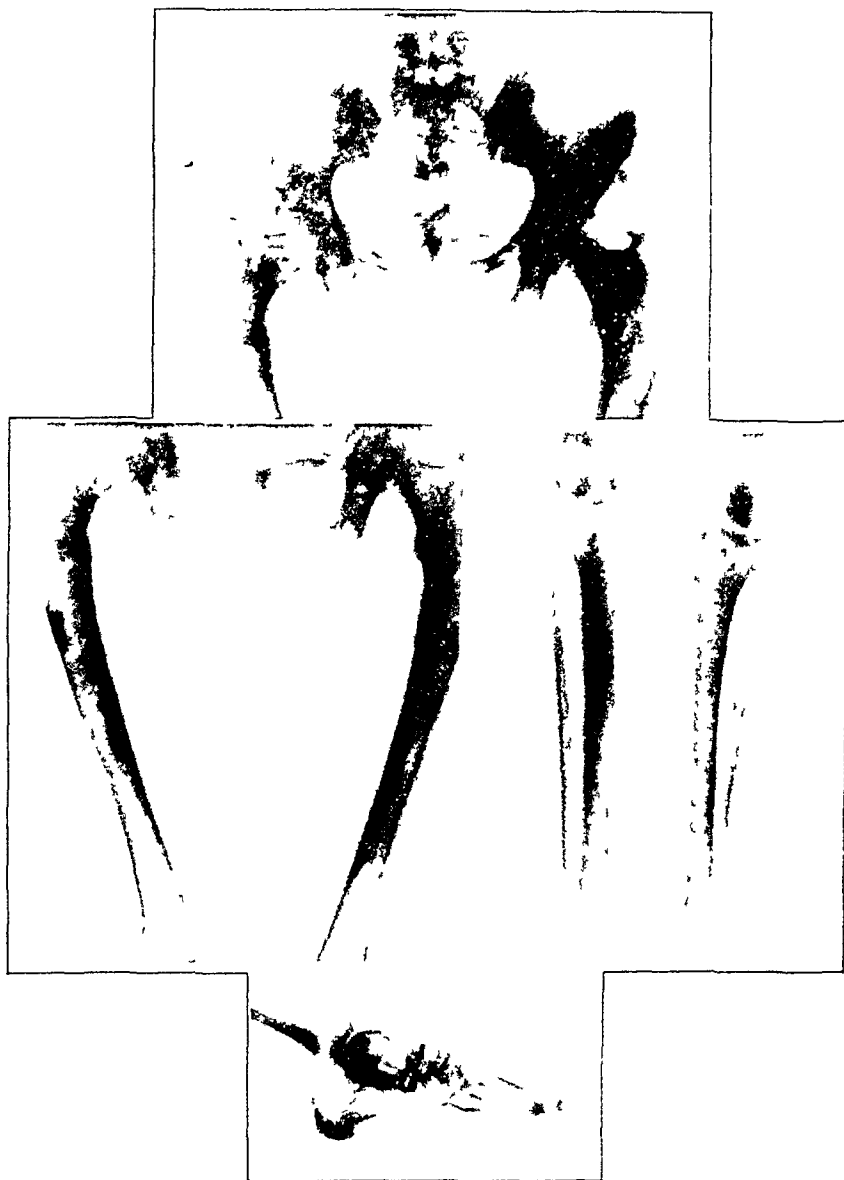


Fig 1—Roentgen changes in the bones

Other Findings The Wassermann and Kahn reactions of the blood were negative. The cholesterol content of the plasma was 119 mg per hundred cubic centimeters. The sugar content of the blood was 76 mg and the urea nitrogen content 10.5 mg per hundred cubic centimeters. The urea clearance of the blood was 51 per cent of the average normal. The dextrose tolerance was normal. The basal metabolic rate was +15 per cent in November 1937 and -17 per cent in July 1938.



Fig 2—Microscopic appearance of biopsy specimen in different magnifications
A, $\times 100$, B, $\times 250$

Biopsy of Bone—On July 5 a piece of bone was removed from the left femur, just below the level of the great trochanter. Grossly, no periosteal reaction was observed, the cortex was extremely thin, and the spongiosa was replaced by a gritty, whitish fibrous tissue which bled slightly. Microscopic examination revealed that the spongy bone had been replaced by, and the marrow cavities filled with, very cellular fibrous tissue in which numerous areas of osteoid tissue and spicules of calcified bone were scattered. No cartilage was noted. Occasional vascular channels were seen, and a moderate number of multinucleated cells were scattered within the fibrous tissue and along the margins of the bone. No evidence of cyst formation was observed (fig 2).

Operation—On September 16 exploration of the neck was performed by Dr George Muller. There was no gross evidence of parathyroid tumor or hyperplasia and no microscopic evidence of parathyroid tissue in a nodular piece of tissue excised from the thyroid gland, which was reported as showing "adenomatous glandular hyperplasia" (Dr B. L. Crawford).

At the time of writing, after ten months of observation, the clinical and roentgenographic pictures have altered only in that the patient has become increasingly disabled by pain and weakness and there has been some progression of the bone lesions. Efforts have been made to control the pain by subarachnoid injections of alcohol, and chordotomy is contemplated if other measures are unsuccessful.

COMMENT

In the opinion of the roentgenologist, the skeletal lesions presented a rather characteristic picture of osteitis fibrosa cystica dependent on a state of hyperparathyroidism. There were certain points, however, which weighed strongly against the diagnosis. Among the more important of these were (1) the comparatively early age of the patient at the onset of symptoms (11 years), (2) the consistently essentially normal serum calcium and phosphorus concentrations and serum phosphatase activity and (3) the absence of excessive excretion of calcium in the urine during periods of low calcium intake. The phosphorus content of the diet during these periods was perhaps not low enough to render this observation as conclusive as it would otherwise have been, but it certainly was not high enough to prevent the characteristic excessive urinary excretion of calcium associated with hyperparathyroidism. Moreover, whereas it is possible that osseous lesions due to previous hyperparathyroidism may persist during periods of remission of the latter state, during which no metabolic evidence of such hyperparathyroidism may be demonstrable, it seems inconceivable that such lesions can progress for ten months with no associated manifestations of abnormal parathyroid function. This diagnosis having been excluded and the clinical course of the condition and the absence of other significant findings apparently having excluded multiple myeloma and metastatic malignant lesions, it was felt that the condition was probably either polyostotic fibrous dysplasia or an atypical skeletal xanthomatous

process. The latter was ruled out by the results of examination of the biopsy specimen.

The characteristic features of the lesion in this case closely resemble those described by Lichtenstein¹ and by Jaffe.² These consist in replacement of the substantia spongiosa and filling of the medullary cavity by fibrous tissue in which sporadic islands of hyaline cartilage and poorly calcified primitive bone develop by metaplasia and in which are distributed small nests of giant cells and occasional vascular channels. The cortex becomes expanded and thinned owing to encroachment on its endosteal surface by the proliferating fibrous tissue. These changes apparently result from perverted development of the bone-forming mesenchyme, and a congenital basis has been suggested. The diagnosis of polyostotic fibrous dysplasia in this case seems justified on the basis of (1) the consistent absence of abnormality of calcium or phosphorus metabolism during a period of progression of the skeletal lesions, (2) the histologic characteristics of the lesion and (3) the failure to detect any abnormality of the parathyroid glands on surgical exploration of the neck. In our opinion, the latter procedure is not justified in such cases.

Dr. H. L. Jaffe assisted in the interpretation of the histologic sections of the biopsy specimen.

[NOTE—The patient in the case reported was rehospitalized in June 1939 for a brief period of observation. She no longer had pain in the left hip and left lower extremity, and the discomfort in the right hip and right lower extremity had lessened considerably. Despite weight bearing for short periods daily, there had been no increase in her deformities. There was no roentgen evidence of alteration in the osseous lesions, and no new lesions were apparent. The laboratory findings corresponded with those previously recorded.]

BOECK'S SARCOID

AUTOPSY IN A CASE WITH VISCERAL LESIONS

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An extensive literature has appeared on the subject of sarcoid since the cutaneous lesions were described by Hutchinson (1869), Besnier (1889) and Boeck (1899). In the majority of the cases reported only the cutaneous manifestations have appeared. Kuznitzky and Bittorf¹ in 1915 suggested that there is a generalized distribution of the lesions, and Jungling² in 1920 and in 1928 published his observations on the osseous changes. These publications prompted a further interest in the character and distribution of the visceral lesions. A comprehensive review of the subject is to be found in the recent publication of Longcope and Pierson³.

Although the disease with generalized lesions has been well studied, only a few autopsies have been reported. Bernstein, Konzelmann and Sidlick⁴ in 1929 reported a case of sarcoid with lesions in the skin, epicardium, bronchial mucosa and mucosa of the ileum. Mylius and Schurmann⁵ in 1929 presented 2 cases. In the first, in which there was an associated pulmonary tuberculosis, iritis had been observed clinically, together with cutaneous lesions on the cheek, cystic changes of the phalanges, enlargement of the mediastinal lymph nodes and infiltration of the lungs. Autopsy revealed lesions in the skin, lungs, liver, lymph nodes and phalanges. In the second case only lesions in the lungs and peribronchial lymph nodes were described. Lenartowicz

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1 Kuznitzky, E, and Bittorf, A. Boecksches Sarkoid mit Beteiligung innerer Organe, *Munchen med Wchnschr* **62** 1349, 1915

2 Jungling, O. Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose), *Fortschr a d Geb d Rontgenstrahlen* **27** 375, 1920, Ueber Ostitis tuberculosa multiplex cystoides, zugleich ein Beitrag zur Lehre von den Tuberkuliden des Knochens, *Beitr z klin Chir* **143** 401, 1928

3 Longcope, W T, and Pierson, J W. Boeck's Sarcoid (Sarcoidosis), *Bull Johns Hopkins Hosp* **60** 223, 1937

4 Bernstein, M, Konzelmann, F W, and Sidlick, D M. Boeck's Sarcoid. Report of a Case with Visceral Involvement, *Arch Int Med* **44** 721 (Nov) 1929

5 Mylius, K, and Schurmann, P. Universelle sklerosierende tuberkulose grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose, *Beitr z Klin d Tuberk* **73** 166, 1929

and Rothfeld⁶ in the same year described a case of sarcoid with lesions in the brain, lungs, spleen, gastrointestinal tract, lymph nodes and bones

Schaumann⁷ in 1936 reported 4 cases in 3 of which a thorough clinical study had been made, in the fourth diagnosis was made post mortem. Active tuberculosis was associated with the sarcoid lesions in 2 of the cases. In the first case the lesions had regressed after the development of the active pulmonary tuberculosis. In the second case lesions appeared in the skin, lungs, epicardium, liver, spleen, capsule of the kidney, lymphatics, phalanges and marrow of the humerus and radius. In the third case clinical diagnosis was based on the character of the lesions of the skin, the enlargement of the lymph nodes, the osseous changes and the enlargement of the hilar shadows. At autopsy lesions were seen in the lungs, subepithelial connective tissue of the trachea, gastrointestinal tract, liver, spleen, epididymis, prostate, lymph nodes and lumbar vertebrae. In this case the active tuberculous peritonitis which was present was considered merely a complication. The author stated that the rapidity of death did not permit fibrosis of the sarcoid lesions. In the fourth case, in which diagnosis was made at autopsy, the lymph nodes, spleen, pharynx, liver and lungs were involved.

In July 1937 Nickerson⁸ published a report of 6 cases of sarcoid with visceral involvement, in all but 1 of which some other disease caused death. In 1 case, that of a middle-aged Negress, death was due to a widespread sarcoid infection, without cutaneous lesions. The clinical diagnosis was atypical tuberculosis of the lungs and lymph nodes and bronchial asthma. The postmortem diagnosis was atypical tuberculosis, but the condition was later considered sarcoid. A few solitary lesions were noted in the myocardium and endocardium in 1 case. Other organs observed to be involved were the lungs, spleen, liver, pancreas, testis, lymph nodes and bone marrow of the femur and vertebrae.

The report of an unusual case in which generalized chronic infectious granulomas involved especially the myocardium is presented. The course was rapid, terminating fatally within eleven weeks of the development of subjective symptoms. Autopsy was performed one hour and a half post mortem. Because of the character and distribution of the lesions and an inability to demonstrate an etiologic agent, the diagnosis of Boeck's sarcoid was made.

6 Lenartowicz, J, and Rothfeld, J. Ein Fall von Hautsarkoiden (Darier-Roussy) mit identischen Veränderungen im Gehirn und den inneren Organen, *Arch f Dermat u Syph* **161** 504, 1930.

7 Schaumann J. Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, *Brit J Dermat* **48** 399, 1936.

8 Nickerson, D. A. Boeck's Sarcoid. Report of Six Cases in Which Autopsies Were Made, *Arch Path* **24** 19 (July) 1937.

REPORT OF A CASE

Clinical History—W L S., a Negro aged 18, was admitted to the Vanderbilt University Hospital on June 21, 1937. His illness had begun insidiously six weeks before admission and had grown progressively worse, even though he had stopped working, in a beer garden, and spent most of his time resting at home. He had been aware first of marked fatigue and dyspnea on exertion. Later he had noticed slight edema of his ankles, orthopnea and a persistent cough, worse at night and productive of mucoid sputum. Even though his appetite had remained good, he had lost weight, although he did not know exactly how much. He had not experienced pain, hemoptysis, night sweats or chills. He had had influenza during the winter of 1936 but stated that he had not had any other illness. He had not been exposed to tuberculosis. His familial history was noncontributory.

Physical Examination—The temperature was 99.2 F, the pulse rate 142 and the respiratory rate 48. The patient appeared critically ill, with labored respiration in both inspiration and expiration. He was poorly nourished, although well developed. There was slight venous congestion. The pupils were normal. The tonsils were enlarged and cryptic. The heart was enlarged, with the point of maximum impulse in the sixth interspace in the anterior axillary line, and there was a cardiac dullness at this level of 5.5 by 12 cm. A distinct precordial bulge and a strong systolic pulsation over the area of the right ventricle were observed. The cardiac rate was rapid, and the first sound had a loud slapping quality. The second sound at the pulmonic area was accentuated and reduplicated. The blood pressure was 140 mm of mercury systolic and 110 diastolic. There were an ascending line of dullness and some suppression of breath sounds in the right axilla. Posteriorly in the midline there was little difference on percussion, and the bases were estimated to occupy a relatively normal position. Numerous rales were heard throughout both lungs, more marked in the lower half, and without definite changes in respiratory sound. The margin of the liver was 3 cm below the right costal margin and was tender on pressure. Slight pitting edema of the lower extremities was present. There was a moderate general glandular enlargement, the nodes being hard, discrete and nontender.

Laboratory Findings—The urine was amber and acid, with a specific gravity of 1.006 to 1.015, a trace of albumin and no sugar. There were a few white blood cells and an occasional red blood cell. Many hyaline and granular casts were present.

The blood count was 3,367,000 red cells, with hemoglobin 11 Gm, and 5,680 white cells. The supravital differential count was polymorphonuclear neutrophilic leukocytes, 72 per cent, polymorphonuclear basophilic leukocytes, 1 per cent, polymorphonuclear eosinophilic leukocytes, 1 per cent, small lymphocytes, 4.5 per cent, intermediate lymphocytes, 4.5 per cent, and monocytes, 17 per cent. Wassermann and Kahn reactions were strongly positive. The total serum protein was 6.62 Gm per hundred cubic centimeters. The albumin fraction was 3.61 Gm and the globulin 3.01 Gm.

The reaction to 0.1 cc of old tuberculin (1:100) was negative after forty-eight hours.

The roentgenograms showed a thickening of the hilus of each lung, with heavy infiltration radiating from the hilus to the periphery and base. The heart was somewhat enlarged, and considerable exudation on both sides extended upward from the bases.

Subsequent Course—The course in general was unsatisfactory, although the patient showed slight improvement at times. Evidence of right ventricular failure

became more marked, and cyanosis of the nail beds appeared. The temperature varied between 98.6 and 100 F, but on several occasions reached 101. The electrocardiographic picture changed from that of sinus tachycardia, with arborization block and low voltage, to that of auricular fibrillation, complete heart block and a shifting pacemaker. The patient died on July 22, of progressive myocardial failure.

Autopsy—*Gross Examination* The body was that of a malnourished Negro of 18, with good skeletal development. The cervical, axillary, inguinal and epitrochlear lymph nodes were slightly enlarged, firm, discrete and movable. The pupils were equal and dilated. The neck, chest and abdomen were not remarkable. A small, firm, movable nodule 1 by 1.5 cm. was present on the flexor surface of the left forearm. There was pitting edema of the ankles. The peritoneum was smooth and glistening. There was 250 cc. of clear straw-colored fluid in the peritoneal cavity. The margin of the liver was 3 cm. below the right costal margin. Fibrous adhesions covered a small nodule in the upper portion of the lower lobe of the left lung and attached the visceral and parietal pleurae at this point. Two hundred cubic centimeters of clear fluid was present in each pleural cavity. The pericardium was smooth, thin and glistening. About 60 cc. of clear fluid was present in the pericardial cavity.

The heart was hypertrophied, weighing 450 Gm. All the chambers were dilated. The myocardium was pale and soft. The myocardium of the left ventricle measured 1.7 cm. The muscle bundles were distorted by numerous irregular opaque yellowish areas, which were seen throughout, occupying a considerable portion of the myocardium. Small, discrete, slightly raised gray nodules, about 2 mm. in diameter, were noted just beneath the endocardium. Several small sessile nodules of a similar appearance were present on the contact surface of the aortic leaflet of the mitral valve. One measured 4 by 2 mm. and the others 2 mm. each. There was no associated shortening, rolling or thickening of the cusps. The cusps of the aortic, the pulmonic and the tricuspid valve were not remarkable. The valves measured: aortic, 5.5 cm., mitral, 9 cm., pulmonic, 6 cm., and tricuspid, 12 cm. Mural thrombi were attached to the endocardium of both ventricles. The coronary vessels were not unusual. The aorta showed no evidence of syphilis or atherosclerosis.

The lungs were heavy, the right weighing 720 Gm., and the left 600 Gm. A firm nodule, measuring 1.5 by 2.5 cm., at the periphery of the upper portion of the lower lobe of the left lung was covered by torn fibrous adhesions and was clearly differentiated from the surrounding parenchyma. The cut surface had a gray, opaque appearance. A smaller nodule of a similar character, measuring 6 mm., was observed in the posterior portion of the same lobe. A number of barely palpable minute nodules were present on the surface of the right lower lobe. The dependent portions of the lungs were firm, and an abundance of frothy fluid exuded onto the cut surface. The hilar and peribronchial lymph nodes were much enlarged, measuring from 1 to 2.5 cm. They were firm, glistening and light gray.

The gastrointestinal tract was not remarkable. Several small, firm, slightly raised gray nodules, about 1 mm. in diameter, were noted on the surface of the liver. The spleen, pancreas and adrenals were of normal size, shape, appearance and consistency. The kidneys were of normal weight and appeared swollen and congested, and each contained a fairly large infarct.

Microscopic Examination The lesions were composed of multiple discrete tubercles as well as many confluent groups of tubercles. The center of the

tubercle was composed of endothelial cells, often associated with a giant cell, and about the periphery there existed a scanty zone of lymphocytes. The giant cells were numerous, often situated at the periphery of the tubercles and frequently containing from twenty to thirty rather irregularly distributed nuclei. In one large giant cell in the myocardium fifty nuclei were counted. When the tubercles



Fig 1—*A*, left ventricular myocardium, showing mottling by gray granulomatous foci and a mural thrombus at the apex. *B*, left lung, showing a peripheral nodule (*a*) and enlarged peribronchial nodes (*b*)

became confluent the typical arrangement was lost, and there was an increase in fibrous tissue, this change could be demonstrated extensively with Mallory's collagen stain. A thin zone of collagen was present about the periphery of many of the solitary tubercles. There were a few lymphocytes but no polymorphonuclear leukocytes.

The myocardium had been extensively replaced by chronic inflammatory granulation tissue, in which there was fibrosis but no caseation. The epicardium had been entirely spared and showed no thickening or infiltration. The tubercles had a milary distribution in the lungs but also coalesced to form nodules, in which

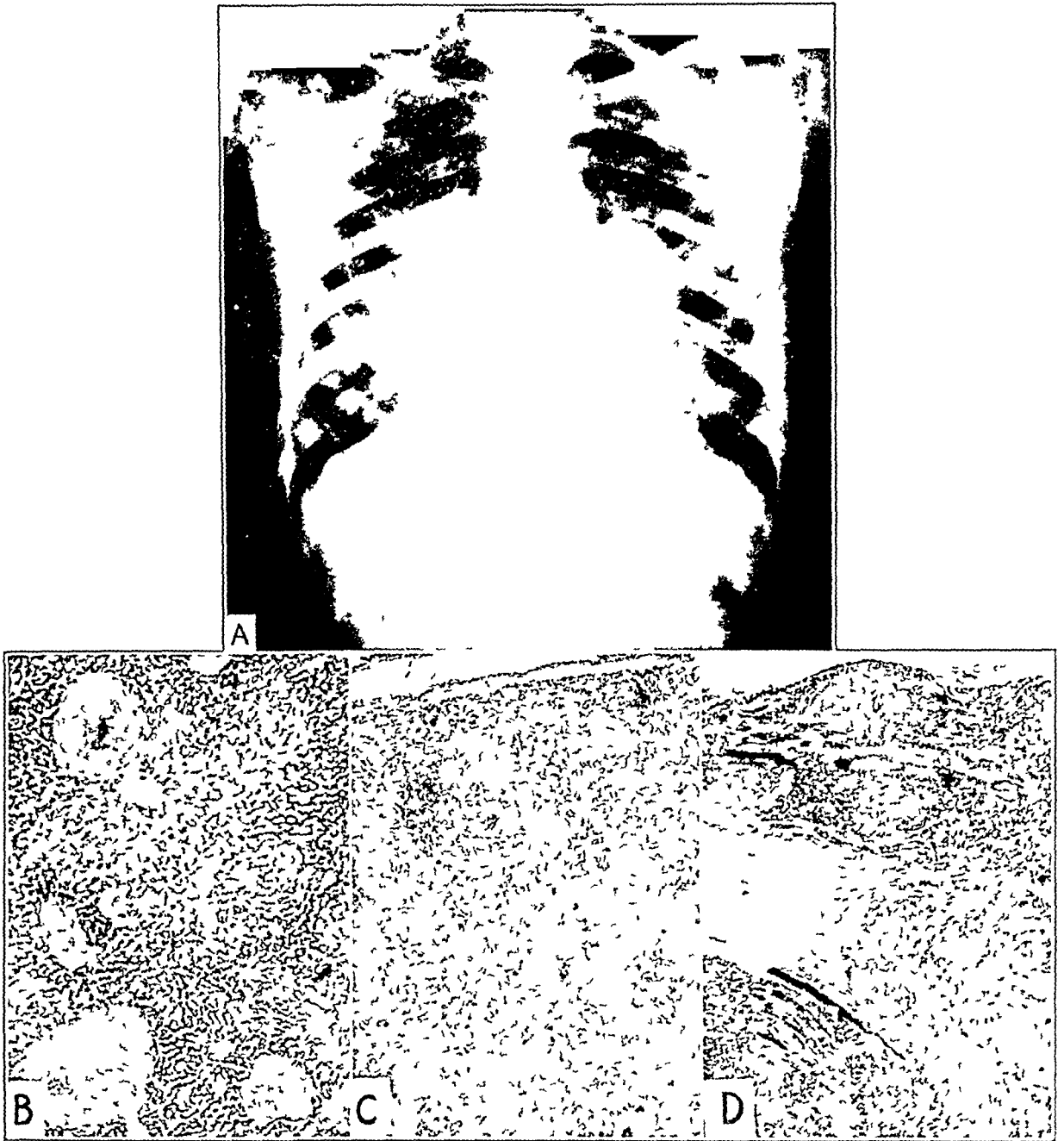


Fig 2—*A*, roentgenogram, showing hilar infiltration. *B*, *C* and *D*, photomicrographs showing, respectively, granulomatous foci in the liver, $\times 32$, a bronchial node, granulomatous infiltration with collagenous degeneration and giant cells, $\times 32$, a subcutaneous nodule with granulomatous infiltration of striated muscle, $\times 32$.

there were much fibrosis and slight lymphocytic infiltration but no caseation. The nodules at the periphery of the lower lobe of the left lung had this type of structure. The peribronchial and hilar lymph nodes were extensively involved.

and small areas of caseation could be seen, but they were indeed scant. Many miliary lesions were observed in the liver, which had mainly a periportal arrangement. A few lesions were observed in the spleen, testicle and wall of the alimentary tract.

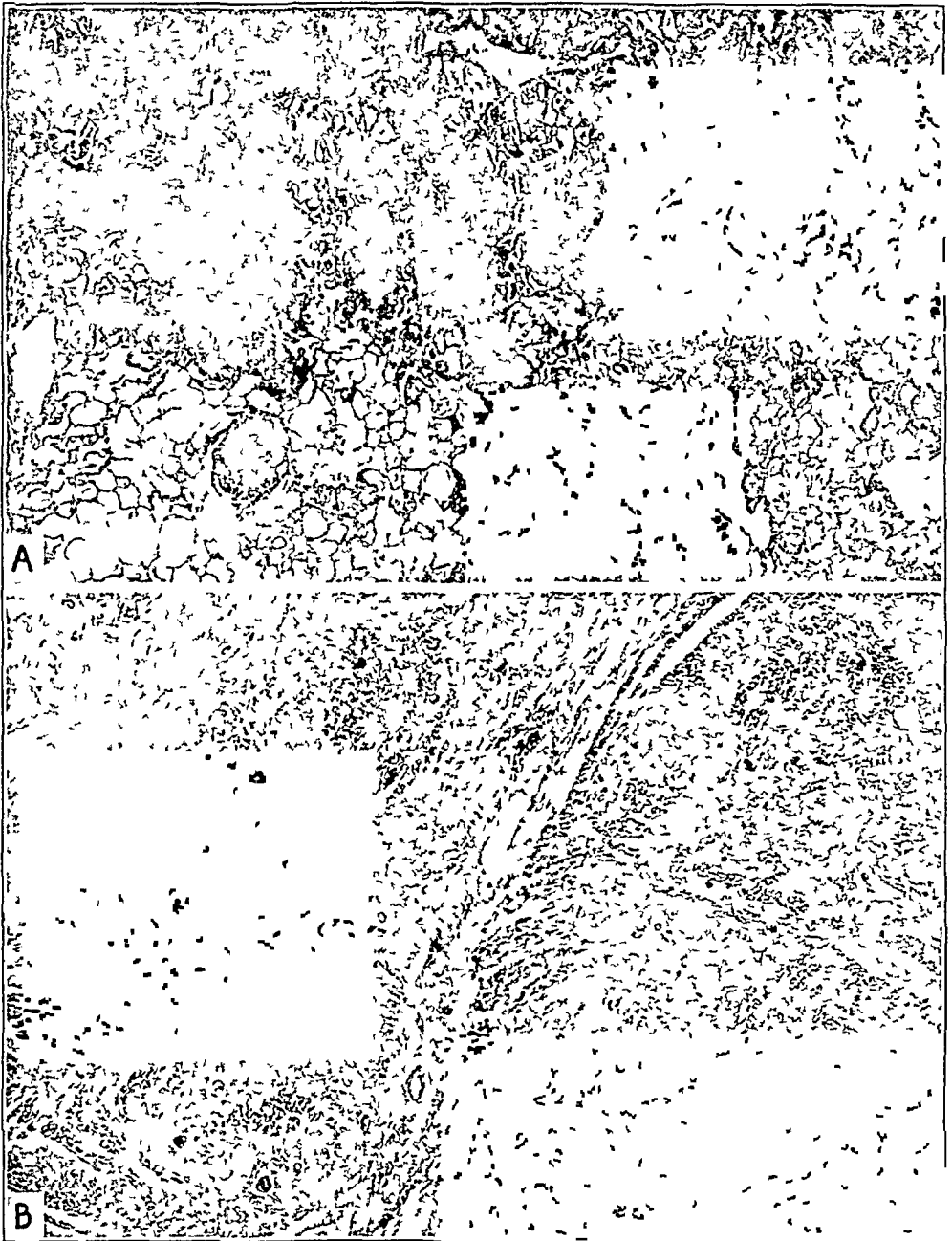


Fig 3—*A*, a section of the left lung through the margin of the granulomatous nodule (*a*, fig 1 *B*), $\times 15\frac{1}{2}$. *B*, a section of the left ventricular myocardium, showing granulomatous infiltration. Numerous giant cells are seen, $\times 28$.

The subcutaneous nodule removed from the left forearm was of particular interest in that it showed the same type of reaction as that described in the heart, lungs and other organs. The nodule extended into the underlying muscle but did not involve the skin.

COMMENT

Clinically, sarcoid is a chronic disease. It persists usually over a number of years, produces only a slight constitutional reaction, seldom responds to treatment, is sometimes recurrent, and most often is associated with a negative tuberculin reaction. The clinical manifestations are characteristic lesions of the skin, enlargement of the superficial lymph nodes and tonsils, widening of the hilar shadows of the lungs, as observed roentgenographically, infiltration of the peripheral fields of the lungs, rhinitis, iridocyclitis, enlargement of the parotid gland, splenomegaly and hepatomegaly. Apparently the tissues of different persons vary markedly in susceptibility. In 1 case the skin may be predominantly involved, in another the lymph nodes and in still another the internal organs. Cutaneous lesions are not present in some cases.

Longcope and Pierson reported a case of Boeck's sarcoid with bilateral iridocyclitis in which also the superficial lymph nodes were enlarged. The lacrimal glands were swollen, and nodules appeared beneath the eyelids and in the parotid glands. Roentgen examination of the chest revealed an enlargement of the hilar shadows and an infiltration of the lungs, particularly on the right side. The authors called attention to the striking resemblance between the condition and that described as uveoparotitis, uveoparotid tuberculosis or uveoparotid fever.

Uveoparotid fever presents the same etiologic problem as sarcoid. It is a chronic condition in which there is mild fever, bilateral uveitis and enlargement of the parotid glands. The disease of the uveal tract usually leads to some impairment of vision, while the parotid glands return to their normal size. Not infrequently there is paralysis of the facial nerve. The tuberculin test is usually negative except in the presence of an active classic tuberculous lesion. Typical cutaneous lesions and osseous changes of sarcoid have not been described as associated with the disease.

Thomson⁹ in 1930 reported a case of uveoparotid fever in which an unusual type of diffuse tuberculous infiltration of the myocardium failed to involve the parietal pericardium. The lesions were described as composed of endothelial cells, lymphocytes and giant cells, without caseation and with demonstrable collagen fibers. Minor lesions were noted in the epicardium, lungs and tracheobronchial and mediastinal lymph nodes. The author was unable to identify the tubercle bacillus in sections but claimed to have observed it after digesting the heart muscle in sodium hydroxide.

⁹ Thomson, J. G. An Unusual Case of Diffuse Tuberculous Infiltration of the Myocardium. *J. Path. & Bact.* **33** 259, 1930.

Garland and Thomson¹⁰ reviewed the literature on uveoparotid fever in 1933 and reported a case in which they found myocardial lesions at autopsy. They considered the condition in their case to be miliary tuberculosis, although they were willing to admit the distribution of the lesions was unusual. They stated that the histologic appearance of the tissue was sufficiently characteristic to warrant a diagnosis of tuberculosis, even though the tubercle bacillus could not be demonstrated. The character of the myocardium was identical with that reported previously by Thomson, and illustrations were included in the publication to stress this point. The absence of caseation was impressive, and collagen fibers could be demonstrated. Lesions were noted in the lungs, liver, kidney, uterus, parotid and submaxillary glands. The peritoneum was markedly involved. There was evidence of an old tuberculous infection of the mesenteric lymph nodes, with caseation and calcification. No lesions were observed in the spleen, on either macroscopic or microscopic examination, which is unusual in cases of miliary tuberculosis.

The classification of my case is based on the character and distribution of the lesions and on my inability to demonstrate an etiologic agent. In typical miliary tuberculosis there is caseation, a primary focus can usually be found, and the tubercle bacilli can be identified in the lesions. The disseminated type of myocardial tuberculosis is rare and represents usually an extension from tuberculous pericarditis. Thomson's case is an exceptional one in this group. In the case I have presented the lesions differed from the classic tuberculous lesions in that they were cellular and contained considerable fibrous tissue and practically no caseation. The myocardium was almost completely replaced by granulation tissue, but the parietal pericardium was not involved. Sections of tissue fixed with solution of formaldehyde and Zenker's solution have been stained for the tubercle bacillus by the Ziehl-Neelsen method, and large pieces of lung, myocardium and lymph nodes have been digested with antiformin (a strongly alkaline solution of sodium hypochlorite) and also with a solution of sodium hydroxide. The centrifuged sediment was then stained for acid-fast bacilli. These attempts to identify the tubercle bacillus have been unsuccessful.

Syphilis has been considered as an etiologic possibility, but it is difficult to imagine the lesions of syphilis having such an unusual distribution and such an extensive myocardial involvement. The duration of syphilis in my case is unknown, but it is known that the patient had never received antisyphilitic therapy. Levaditi stains of autopsy material were prepared on two occasions and negative results obtained in each instance.

¹⁰ Garland, H. G., and Thomson, J. G. Uveo-Parotid Tuberculosis, *Quart J Med* 2: 157, 1933.

In Nickerson's case of acute fulminating sarcoid which was first thought to be an instance atypical tuberculosis, the picture resembled that in my case in many respects. Nickerson stated that a small amount of fibrinoid material in the lesions is consistent with the diagnosis of sarcoid for such fulminating conditions.

The remarkable similarity between the myocardial lesions in the 2 reported cases of uveoparotid fever and those in the present case may indicate some relation between the two conditions. From a clinical aspect this relation has been suggested by Longcope and Pierson, who indicated that uveoparotid fever may be merely a clinical variation of sarcoid.

I do not feel that there is sufficient justification to diagnose tuberculosis in my case, and the evidence presented has led me to believe that the condition can most satisfactorily be considered Boeck's sarcoid.

SUMMARY

A disseminated, chronic, infectious granuloma is reported occurring in a young Negro. The outstanding features are the character and extent of the myocardial involvement. The case is considered one of Boeck's sarcoid, with visceral involvement, without typical cutaneous manifestations and without active classic tuberculosis.

The similarity between the myocardial lesions in this case and those in 2 cases of uveoparotid fever is impressive.

CARDIAC SEQUELAE OF EMBOLISM OF THE PULMONARY ARTERY

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A number of clinical observations have indicated that some of the serious consequences of embolism of the pulmonary artery are due to a deleterious effect on the heart and the coronary circulation. Extensive occlusion of the pulmonary circulation is usually followed by circulatory shock and an associated diminution in the cardiac output. The usual symptom complex of embolism of the pulmonary artery, which is characterized by marked dyspnea, cyanosis, tachypnea, substernal oppression, collapse of the peripheral circulation, apprehension, feeble pulse, profuse perspiration, ashen pallor and low blood pressure, is frequently indistinguishable from the clinical picture observed in coronary occlusion with myocardial infarction. This striking similarity in itself suggests the possibility that the syndrome of embolism of the pulmonary artery may actually result from a diminution of the coronary circulation and associated ischemia of the myocardium. The characteristic electrocardiogram in cases of embolism of the pulmonary artery is frequently identical with or almost indistinguishable from that in cases of infarction of the posterior wall of the left ventricle. The frequency and the nature of these electrocardiographic abnormalities further suggest that the heart is the site of a secondary ischemic alteration. In some cases, sudden death following multiple small emboli in relatively few branches of the pulmonary artery cannot be reasonably ascribed to a significant interference with the pulmonary circulation. A reflex or secondary effect on the coronary circulation and myocardium has consequently been invoked to explain such an occurrence.

PATHOGENESIS OF CARDIAC SEQUELAE AND CAUSE OF DEATH IN EMBOLISM OF THE PULMONARY ARTERY

On the basis of numerous experimental and clinical observations, a number of mechanisms have been adduced to explain the manner in which embolism of the pulmonary artery may affect the circulation and

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cause death. It is extremely difficult to dissociate the individual factors concerned, partly because several of them may act simultaneously and partly because they have an important influence on each other. For purposes of discussion, however, the various factors may be analyzed individually. The main cardiac effects of embolism of the pulmonary artery are due either (A) to mechanical obstruction of the pulmonary artery with strain on the right ventricle or (B) to myocardial ischemia. The latter may result from shock, generalized anoxemia or vagal reflexes from the lungs to the coronary vessels.

A Obstruction of the Pulmonary Artery—The mechanical effect of embolism of the pulmonary artery on the circulation may be ascertained from the results obtained by experimental occlusion of this artery or its branches. Various experiments¹ have shown that extreme degrees of obstruction of the pulmonary artery (80 per cent of the lumen or more) are necessary to effect a significant reduction in the systemic blood pressure or to cause death. At the same time, almost complete occlusion of the pulmonary artery induces dilatation of the right ventricle. While more moderate degrees of obstruction of the artery are not followed by dilatation of the right ventricle, they may increase the pressure within that chamber as well as in the pulmonary artery proximal to the obstruction. Thus moderate obstruction of the pulmonary artery may result in evidence of strain on the right ventricle even when there is no visible dilatation.²

Clinical observations on human beings indicate that in many instances of embolism of the pulmonary artery there is actually sufficient mechan-

1 (a) Welch, W. H. Zur Pathologie des Lungenödems, *Virchow's Arch f. path. Anat.* **72** 375, 1878. (b) Gerhardt, D. Experimentelle Beiträge zur Lehre vom Lungenkreislauf und von der mechanischen Wirkung pleuritischen Ergusses, *Ztschr. f. klin. Med.* **55** 195, 1904. (c) Mann, F. C. Pulmonary Embolism, *J. Exper. Med.* **26** 387, 1917. (d) Dunn, J. S. The Effects of Multiple Embolism of the Pulmonary Arterioles, *Quart. J. Med.* **13** 129, 1920. (e) Tigerstedt, R. Die Physiologie des Kreislaufes, Berlin, W. de Gruyter & Co., 1923. (f) Schlaepfer, K. Ligation of the Pulmonary Artery of One Lung With and Without Resection of the Phrenic Nerve, *Arch. Surg.* **9** 25 (July) 1924. (g) Haggart, G. E., and Walker, A. M. Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, *ibid.* **6** 764 (May) 1923. (h) Gibbon, J. H., Jr., Hopkinson, M., and Churchill, E. D. Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, *J. Clin. Investigation* **11** 543, 1932. (i) Hall, G. E., and Ettinger, G. H. An Experimental Study of Pulmonary Embolism, *Canad. M. A. J.* **28** 357, 1933. (j) Gibbon, J. H., Jr., and Churchill, E. D. Physiology of Massive Pulmonary Embolism, *Ann. Surg.* **104** 811, 1936. (k) Jackson, D. E., and Jackson, H. L. Physiologic Consideration Regarding the Etiology and Nature of Coronary Thrombosis, *J. Lab. & Clin. Med.* **22** 329, 1937.

2 Fineberg, M. H., and Wiggers, C. J. Compensation and Failure of the Right Ventricle, *Am. Heart J.* **11** 255, 1936. Haggart and Walker ^{1g}

ical obstruction to produce dilatation of the right side of the heart and significant diminution in cardiac output and systemic blood pressure. In such instances, the embolic mass either blocks the main stem of the pulmonary artery or exists as multiple foci, occluding the lumens of several smaller branches and producing thereby a similar effect. McGinn and White³ applied the term acute cor pulmonale to a clinical picture which they said was due to the sudden dilatation of the right side of the heart incident to a high degree of obstruction of the pulmonary artery. Of 8 of their patients with embolism of the pulmonary artery, dilatation of the artery was observed in all but 3. The absence of dilatation in the 3 cases was attributed to failure of the right ventricle, shock or the inability of blood to pass beyond the area of obstruction. Churchill⁴ also reported observations on patients operated on for embolism of the pulmonary artery in whom the artery was greatly distended, but he occasionally noted that the arteries were collapsed. He explained the latter observation as indicative of failure of the right ventricle. Earlier reports of marked dilatation of the pulmonary artery following embolism may be cited.⁵

Additional evidence of the mechanical effect of embolism of the pulmonary artery on the right side of the heart resides in the following clinical and electrocardiographic observations. White and his associates⁶ and Lord⁷ noted an accentuation of the second pulmonic sound, which they interpreted as indicating increased pressure in the pulmonary artery. Similarly, they, as well as Litten,⁸ reported a thrill and a to and fro murmur over the pulmonic area due to obstruction to the outflow of blood from the right ventricle and dilatation of the pulmonary artery. Gallop rhythm was attributed to the same cause. Mention was made

3 McGinn, S., and White, P. D. Acute Cor Pulmonale Resulting from Pulmonary Embolism. Its Clinical Recognition, *J A M A* **104** 1473 (April 27) 1935

4 Churchill, E. D. The Mechanism of Death in Massive Pulmonary Embolism, *Surg, Gynec & Obst* **59** 513, 1934

5 Farr, C. E., and Spiegel, R. Pulmonary Infarction and Embolism, *Ann Surg* **89** 481, 1929. Hampton, H. H., and Wharton, L. R. Venous Thrombosis, Pulmonary Infarction and Embolism Following Gynecological Operations, *Bull Johns Hopkins Hosp* **31** 95, 1920

6 (a) White, P. D., and Brenner, O. Pathological and Clinical Aspects of the Pulmonary Circulation, *New England J Med* **209** 1261, 1933. (b) White, P. D. The Acute Cor Pulmonale, *Ann Int Med* **9** 115, 1935. (c) McGinn and White³

7 Lord, F. T. Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1925, p. 483

8 Litten, M. Ueber Verengerungen im Stromgebiet der Lungenarterie, über deren Folgen und die Möglichkeit dieselben während des Lebens zu diagnostizieren, *Berl klin Wchnschr* **19** 425, 1882

also of the occurrence of failure of the right side of the heart in cases of embolism of the pulmonary artery as a result of the increased load on the right ventricle. The chief evidence of this was the engorgement of and elevation of pressure in the superficial veins of the neck. Finally, electrocardiograms made in cases both of experimental obstruction of the pulmonary artery⁹ and of embolism of the artery in man¹⁰ not infrequently revealed the development of deviation of the electrical axis to the right, a large S_1 and a negative T_3 wave, all of which may be considered evidence of strain on the right ventricle.

B Myocardial Ischemia—Sudden obstruction of the pulmonary artery leads to a number of changes which tend to produce myocardial ischemia. The ischemia may be effected by three factors, namely, (1) shock, which is associated with a diminution of the cardiac output and the systemic blood pressure, (2) anoxemia resulting from interference with the pulmonary circulation and diminished oxygenation of the blood, and (3) reflexes by way of the vagus nerve, which may produce a diminution of the caliber of the coronary artery and the blood supply to the myocardium.

1 Shock is a frequent clinical feature in cases of embolism of the pulmonary artery. In such cases there is a marked fall in blood pressure and cardiac output, occasionally to the point where neither the blood pressure nor the pulse can be obtained. These cases correspond to the experiments in which almost the entire pulmonary vascular bed has been occluded. The direct effect of the marked diminution in blood pressure (and consequently in aortic pressure) is to reduce markedly the coronary blood flow. In addition, reduced blood pressure may indirectly cause myocardial anoxemia by interfering with the pulmonary aeration of the blood and by possible reflex influence on the coronary arteries, which will be discussed later.

2 Asphyxia is another common accompaniment of embolism of the pulmonary artery, and not infrequently pronounced degrees of dyspnea

9 (a) Otto, H. L. The Effect of a Sudden Increase in the Intracardiac Pressure upon the Form of the T-Wave of the Electrocardiogram, *J Lab & Clin Med* **14** 643, 1929. (b) Cripes, L. H. Electrocardiographic Studies of the Effect of Anaphylaxis on the Cardiac Mechanism, *Arch Int Med* **48** 1098 (Dec) 1931. (c) Anderson, J. P. Electrocardiographic Findings in Experimental Pulmonary Embolism, abstracted, *Am Heart J* **9** 104, 1933. (d) Buchbinder, W. C., and Katz, L. N. The Electrocardiogram in Acute Experimental Distension of the Right Heart, *Am J M Sc* **187** 785, 1934. (e) McGinn and White.³

10 Langendorf, R., and Pick, A. EKG-Befunde bei Lungenembolie, *Acta med Scandnav* **90** 289, 1936. Barnes, A. R. Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, *Proc Staff Meet, Mayo Clin* **11**, 11, 1936. Pulmonary Embolism, *J A M A* **109** 1347 (Oct 23) 1937. McGinn and White.³

and cyanosis are striking clinical manifestations¹¹ Experimentally, Gibbon and Churchill¹³ noted that while the blood pressure did not fall, even with occlusion of 85 per cent of the pulmonary vascular bed, a distinct oxygen unsaturation of the arterial blood occurred when more than 40 per cent of the pulmonary vascular bed had been occluded The occurrence of varying grades of asphyxia could explain many of the clinical and experimental features of embolism of the pulmonary artery, for these, as well as the electrocardiographic changes observed, are similar to or identical with the manifestations of asphyxia produced by factors other than embolism Crippe^{9b} observed that in the rabbit the cardiac changes following acute asphyxia and those following clamping of the pulmonary artery are essentially the same McGinn and White³ noted that the electrocardiographic changes following occlusion of the pulmonary artery in cats were similar to those observed in asphyxiated cats by Lewis and Mathison¹² Furthermore dilatation of the right chambers of the heart may also be attributed to asphyxia,³ but it is difficult to dissociate this factor from the possible mechanical effect of vascular obstruction in embolism

3 The evaluation of the importance of reflexes in controlling the coronary blood flow, as recently emphasized by Wiggers,¹³ is beset with many difficulties Although the presence in the vagus and sympathetic nerves of fibers for vasomotor control to the coronary arteries is well established, there is some difference of opinion as to their exact distribution in these nerves The weight of opinion¹⁴ appears to indicate that the constrictor fibers to the coronary artery are found in the vagus nerve and the dilator fibers in the sympathetic Anrep and Segall^{14c} found that the coronary flow increased after section of the vagus nerve

11 (a) Edens, E Die Krankheiten des Herzens und der Gefasse, Berlin, Julius Springer, 1929 (b) Averbuck, S H The Differentiation of Acute Coronary Artery Thrombosis from Pulmonary Embolization, *Am J M Sc* **187** 391, 1934 (c) Master, A M, Jaffe, H L, and Dack, S The Clinical and Electrocardiographic Differentiation of Coronary Thrombosis from Pulmonary Embolism, *J Mt Sinai Hosp* **3** 288, 1937

12 Lewis, T, and Mathison, G C Auriculoventricular Heart-Block as a Result of Asphyxia, *Heart* **2** 47, 1910

13 Wiggers, C J The Physiology of the Coronary Circulation, in Levy, R L Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936

14 (a) Porter, W T The Vasomotor Nerves of the Heart, Boston M & S J **134** 39, 1896 (b) Wiggers, C J The Innervation of the Coronary Vessels, *Am J Physiol* **24** 391, 1909 (c) Anrep, G V, and Segall, H N The Regulation of the Coronary Circulation, *Heart* **13** 239, 1926 (d) Rein, H Die Physiologie der Coronardurchblutung, *Verhandl d deutsch Gesellsch f inn Med* **43** 246, 1931 (e) Greene, C W The Nerve Control of the Coronary Vessels, *Am J Physiol* **113** 361, 1935

while it diminished when the vagus nerve was stimulated with the heart rate controlled. These observations have been corroborated by Rein,^{14d} Wiggers¹³ and others, who have shown in addition that the vasoconstrictor effect of vagal stimulation on the coronary arteries could be abolished by atropine. Other observations¹⁵ appear to show that the coronary flow is affected by a change in heart rate and blood pressure. It is possible that the effect of vagal stimulation also may be mediated through changes in rate and blood pressure, rather than through a vasoconstrictor effect.

Edens^{11a} attributed some importance to vagal influence in embolism of the pulmonary artery and expressed the opinion that cardiac dysfunction and death are due to vagal stimulation rather than to obstruction of the artery. A significant relation of embolism of the pulmonary artery to cardiac function via reflex effect is suggested by certain experimental studies. Direct or reflex stimulation of the endings of the vagus nerve in the lungs or pleura of animals has been shown¹⁶ to result in a decrease in heart rate and blood pressure. Strueft^{16c} and Villaret and his co-workers¹⁷ demonstrated that a more significant reflex effect on the heart resulted from small rather than from large emboli of the pulmonary arteries. The latter authors expressed the belief, further, that such reflex effects from stimulation of the terminals of the vagus nerve in the pulmonary arterioles are responsible for sudden death from embolism when there is relatively little obstruction of the pulmonary vascular bed.

Recently Scherf and Schonbrunner¹⁸ attempted to demonstrate the importance of vagal reflexes in dogs by producing embolization of the pulmonary artery without significant obstruction of the pulmonary circulation. Despite removal of the obstructive factor, significant electrocardiographic changes such as are seen in embolism of the pulmonary artery in man were observed in 2 of 10 dogs. The investigators con-

15 Miller, G. H., Smith, F. M., and Graber, V. C. The Influence of Changes in the Cardiac Rate and Irregular Action of the Heart on the Coronary Circulation, *Am Heart J* **2** 479, 1927.

16 (a) Brodie, T. G., and Russel, A. E. On Reflex Cardiac Inhibition, *J Physiol* **26** 92, 1900-1901. (b) Capps, J. A., and Lewis, D. Observations upon Certain Blood-Pressure Lowering Reflexes That Arise from Irritation of the Inflamed Pleura, *Am J M Sc* **134** 868, 1907. (c) Strueft, N. Zur Frage der bakteriellen Lungenembolie, *Virchows Arch f path Anat* **198** 211, 1909.

17 Villaret, M., Justin-Besançon, L., and Bardin, P. *Physio-pathologie des accidents mortels consécutifs aux embolies pulmonaires*, *Bull et mem Soc med d hôp de Paris* **52** 936, 1936, *Recherches sur la prévention expérimentale des accidents consécutifs aux embolies pulmonaires*, *ibid* **52** 941, 1936.

18 Scherf, D., and Schonbrunner, E. (a) Ueber Herzebefunde bei Lungenembolien, *Ztschr f klin Med* **128** 455, 1935, (b) Ueber der pulmocoronaren Reflex bei Lungenembolien, *Klin Wchnschr* **16** 340, 1937.

cluded that these changes had resulted from diminution in the coronary flow produced reflexly by reaction of constrictor fibers in the vagus nerve

From the foregoing evidence, it seems that vasomotor reflexes may play a significant role in the effect of embolism of the pulmonary artery on coronary flow and cardiac action. Direct evidence of the importance of these reflexes in this condition in man is lacking. Their possible effect is confused by the many simultaneous changes which are induced. Thus, even if one accepts the belief that embolism of the pulmonary artery diminishes the coronary flow by vagal stimulation, the concomitant fall in blood pressure and increase in cardiac rate, as well as the reduction in cardiac output and anoxemia, would tend to modify the effect. Furthermore, the reflex stimulus, if present, would not only affect the coronary flow but would also induce a cardiomnhibitory action on the heart with slowing of the heart rate, delay in conduction and possibly even cardiac standstill.

Most observers have failed to note any organic myocardial alterations which might be anticipated as a result of the obstructive, anoxemic and reflex factors discussed. In many of the reports of cases of embolism of the pulmonary artery in which there were postmortem examinations a distinct statement is made that the coronary arteries were patent and that the myocardium showed no significant abnormality which could be ascribed to the embolism. Recently Kroetz and his co-workers¹⁹ reported that the hearts of 12 patients who had died of embolism of the pulmonary artery showed no fresh, ischemic necrosis of the myocardium, except when thrombotic arterial occlusion was associated. In the absence of detailed protocols and descriptions, especially as to the location and extent of the emboli and the duration of life after embolization, we cannot comment on these observations. The statement that abnormal electrocardiographic signs were not demonstrable after repeated embolization of the pulmonary artery in dogs is contrary to the experience of other investigators.⁹

On the other hand, we have been able to find 2 reports in the literature in which mention is made of myocardial changes following obstruction of the pulmonary artery. Boswell and Palmer²⁰ observed a case of progressive thrombosis of the pulmonary artery in which subendocardial myocardial degeneration and fragmentation were noted in the

19 (a) Eckardt, in discussion on Thaddea, S. Ueber Elektrokardiogrammveränderungen im Nebennierencoma und ihre Beeinflussung durch das Nebennierenrindenhormon, *Verhandl d deutsch Gesellsch f inn Med* **48** 354, 1936
(b) Kroetz, C. Das Herz bei akuten Störungen der Lungendurchblutung und der Lungenbeatmung, abstracted, *Klin Wchnschr* **17** 366, 1938

20 Boswell, C H, and Palmer, H D. Progressive Thrombosis of the Pulmonary Artery, *Arch Int Med* **47** 799 (May) 1931

absence of coronary occlusion. Hamburger and Saphir²¹ described an instance (their case 4) of embolism of the pulmonary artery in which a myocardial infarct was associated with coronary sclerosis, but without acute coronary occlusion.

MATERIAL AND METHODS

In a study of the hearts in 42 cases of embolism of the pulmonary artery we observed acute ischemic myocardial damage in 8 (table). Since systematic and diligent search failed to reveal recent coronary occlusion in any of these, we believe the myocardial damage may be related to embolism of the pulmonary artery. In 2 of the hearts there were minute but grossly visible focal areas of necrosis. In the remaining hearts with recent myocardial damage the abnormalities were discovered only after a detailed histologic study.

The hearts which revealed recent myocardial changes and some of those which did not were studied in the fresh state as well as after fixation. On the other hand, many of the hearts in which no such abnormalities were observed at the time of autopsy either were available only as fixed specimens or were not obtainable for reexamination. When the hearts were not available for examination the data were based on the routine protocol descriptions and on restudy of the routine slides which had been saved. In the other instances the specimen was studied in the following manner:

All the major branches of the coronary arteries were systematically investigated. Transverse sections were made throughout the course of each branch at intervals of 2 to 3 mm. Any suspicious site was sectioned in greater detail and studied histologically. Whenever possible, the following branches were cut: the left anterior descending artery and its primary and secondary rami, the left circumflex artery and its branches to the anterior wall of the left ventricle, to the obtuse margin of the heart and to the posterior wall of the left ventricle, the main right coronary artery, the right circumflex artery and its branches to the posterior interventricular sulcus and to the posterior wall of the left ventricle, and the branches of the right coronary artery to the anterior and posterior walls of the right ventricle and to the acute margin of the heart. The branches to the auricles were also examined but were frequently of minute caliber or could not be followed. In addition to searching for occlusion of the coronary arteries, we noted the degree of sclerosis and narrowing of these vessels and their ostia and graded the changes as 1 to 4 plus according to severity.

The various portions of the myocardium were examined systematically for gross abnormalities; notes were made of the appearance of the anterior and posterior walls of the various cardiac chambers, of the left and right sides of the interventricular septum and of the papillary muscles. Then histologic sections were made from each of these regions, particularly from those areas which we suspected on gross examination to be abnormal. Finally, the pericardium, the endocardium and the valves were observed for abnormalities and the weight of the heart and the size of the cardiac chambers noted. The clinical history

21 Hamburger, W. W., and Saphir, O. Pulmonary Embolism Complicating and Simulating Coronary Thrombosis, *M. Clin. North America* 16: 383, 1932.

Anatomic Data on Eight Cases of Recurrent Pulmonary Embolism with Cardiac Damage

Case No	Age, Yr	Weight of Heart, Gm	Cardiac Dilatation*		Coronary Arteries		Anterior Wall of Left Ventricle	Posterior Wall of Left Ventricle	Inter-ventricular Septum	Anterior Wall of Right Ventricle	Posterior Wall of Right Ventricle	Auricles	Cause of Death	Associated Lesions
			Right	Left	Scle	Nar	Anterior Wall of Left Ventricle	Posterior Wall of Left Ventricle						
1	54	430	A + V 0	+	0 to +	0	Foci of necrosis, myodegen fatty change ++	Foci of necrosis with polymorpho nuclears young, edematous connective tissue	Fatty change	Local myodegen erition fatty change	Same as anterior wall plus focal necrosis	Minimal changes	Embolus of pulmonary artery	Thrombosis of common iliac, femoral and hypogastric veins edema of lower extremities essential hypertension hypertrophy of all cardiac chambers
2	41	350	A +++ V ++	+	++	++ to +++	Focal necrosis mesenchymal cell proliferation patchy fibrosis, sub endocardial hemorrhage	Focal necrosis hemorrhage vacuolar changes, fatty changes patchy fibrosis	Focal fine necrosis, polymorpho nuclears interstitial hemorrhage	Degenerative changes polymorpho nuclears	Degenerative changes polymorpho nuclears	0	Embolus of pulmonary artery	Hypertrophy of left ventricle acute congestion of liver and spleen
3	58	165	A +++ V ++	0	+	0	Subendocardial intimal changes	Patchy young connective tissue	Focal necrosis, fatty change, vacuolation, polymorpho nuclears, edematous young connective tissue	Patchy young connective tissue	0	0	Embolus of pulmonary artery	Two carcinomas of large intestine, with metastases to mesentery omentum and liver pulmonary arteriosclerosis hydrothorax (200 cc) on left
4	75	400	A 0 V +	0	+++	+++ to ++++	Focal necrosis and hemorrhage polymorpho nuclears	Fatty change + fibrosis	Focal necrosis with polymorpho nuclears interstitial hemorrhage fatty change	Focal hemorrhage (fine)	0	Fine fibrosis fatty change +++	Embolus of pulmonary artery cardiac failure	Hypertrophy of heart myofibrosis with aneurysmal dilatation of left ventricle, nephrosclerosis, bilateral hydrothorax

5	65	380	A +++ V 0	+	++	++	Focal hemorrhage subendocardial myode generation	Myode-generation focal lymphocytes	Young connective tissue focus	Minute focal necrosis with polymorpho nuclears and lymphocytes	Patchy myodegeneration	0	Embolus of pulmonary artery	Hypertrophy of both ventricles status 11 days after ligation of vas and 45 min after trans urethral prostatectomy, pulmonary infarct in lower lobe of left lung
6	55	300	A + V +	+	+	0	Myode generation (slight) patchy fibrosis	Focal interstitial hemorrhage myodegeneration with polymorpho-nuclears and lymphocytes mainly sub endocardial	Minute focal areas of necrosis with polymorpho nuclears, sub endocardial	0	0	Myodegeneration	Embolus of pulmonary artery pulmonary edema	Eleven days after mastectomy, acute congestion of liver chronic cholecystitis
7	64	560	A ++ V +++	++	+++	+++ to ++++	Foci of hemorrhage fibrosis	Minute focal necrosis myodegeneration, interstitial focus of polymorphonuclears	0	0	0	Fibrosis	Embolus of pulmonary artery cardiac failure	Old infarct of anterior wall of left ventricle mural thrombosis of right auricular appendage and both ventricles
8	70	470	A ++ V ++	++	++	++	Myodegeneration with polymorpho nuclears	Foci of interstitial hemorrhage fibrosis	0	Tinctorial change	0	Fibrosis	Cardiac failure	Hypertrophy and dilatation of heart thrombosis of left auricular appendage, pulmonary infarct thrombosis of iliac veins

* A -- auricle V -- ventricle

and the extracardiac pathologic changes were studied in order to evaluate the role of various possible factors in the production of myocardial disease and coronary insufficiency. In the selection of our cases those were eliminated from study in which there was evidence of infection because of the possible effect of such infection on the myocardium.

REPORT OF CASES

The following are protocols of 4 of the 8 cases in which acute ischemic myocardial changes were observed without concomitant recent coronary occlusions. For the sake of brevity, 4 of the cases, in which there were definite but less marked myocardial alterations, are omitted from detailed consideration.

CASE 1—A woman aged 54 had been observed for four years because of hypertensive heart disease. During this period she suffered from precordial pressure, dyspnea on exertion, attacks of nocturnal dyspnea, headaches, vertigo and weakness. The systolic blood pressure had ranged between 200 and 250 and the diastolic pressure between 100 and 130 mm of mercury. Electrocardiograms (fig 1A) had revealed left axis deviation, high voltage of the QRS complex, depression of the RS-T intervals in leads I and II and inversion of T₁, T₂ and T₄. These changes were ascribed to enlargement of the left ventricle. Three weeks before admission to the hospital she suffered right hemiplegia. Four days before admission nausea, vomiting, weakness and increasing dyspnea had developed.

Examination on admission revealed a pale, drowsy woman. Her heart was moderately enlarged to the left, and her heart sounds were of poor quality. A loud, harsh systolic murmur and a systolic thrill over the entire precordium were now present. The blood pressure had fallen to 130 mm of mercury systolic and 80 mm diastolic. An electrocardiogram (fig 1B) showed partial heart block, with frequent dropped beats. The RT transitions were now markedly depressed in leads I, II and IV. The following day the heart block disappeared, but the marked tachycardia and the deviations of the RT transition persisted (fig 1C).

On the day after admission the patient's blood pressure dropped to 88 mm of mercury systolic and 70 mm diastolic, the temperature rose to 101.6 F, and the leukocyte count to 20,000 per cubic millimeter. She became more dyspneic and cyanotic, the respiratory rate rose to 50, and numerous moist rales appeared in both lungs. Cheyne-Stokes respiration developed, and the patient died three days after admission.

The postmortem diagnosis was thrombosis of the common, external and internal iliac veins, with repeated embolization of the pulmonary arteries, infarction of the lower lobes of the lungs, hypertrophy of the heart, with dilatation of the auricles, slight coronary arteriosclerosis without narrowing, focal myocardial infarction, and chronic cholecystitis and cholelithiasis, with focal fatty necrosis of the pancreas.

The heart appeared moderately enlarged and weighed 430 Gm. The right auricle was dilated and its musculature somewhat thickened. The wall of the right ventricle was slightly hypertrophied, but there was no dilatation of the right ventricular chamber. Immediately proximal to the pulmonary conus was pronounced bulging of the interventricular septum into the cavity of the right ventricle. The pulmonic ring was not widened. A coiled, tubular, gray-red

thrombus, with dull and granular surface, filled the main stem of the pulmonary artery. It extended from the level of the pulmonic ring into the left pulmonary artery and its branches, but only slightly into the right pulmonary stem. The embolus in the left pulmonary artery was seen to be adherent to the intima of that artery and its smaller divisions. The wall of the left auricle was slightly, and that of the left ventricle markedly, hypertrophied. The subendocardial portion of the myocardium, especially in the interventricular septum and the papillary muscles, but also along the anterior and the septal aspect of the left ventricle, showed yellowish brown and moist red mottling. Similar changes of less degree were observed in the right ventricular subendocardial myocardium. Fine gray perivascular streaks were scattered in the deeper portions of the left ventricular

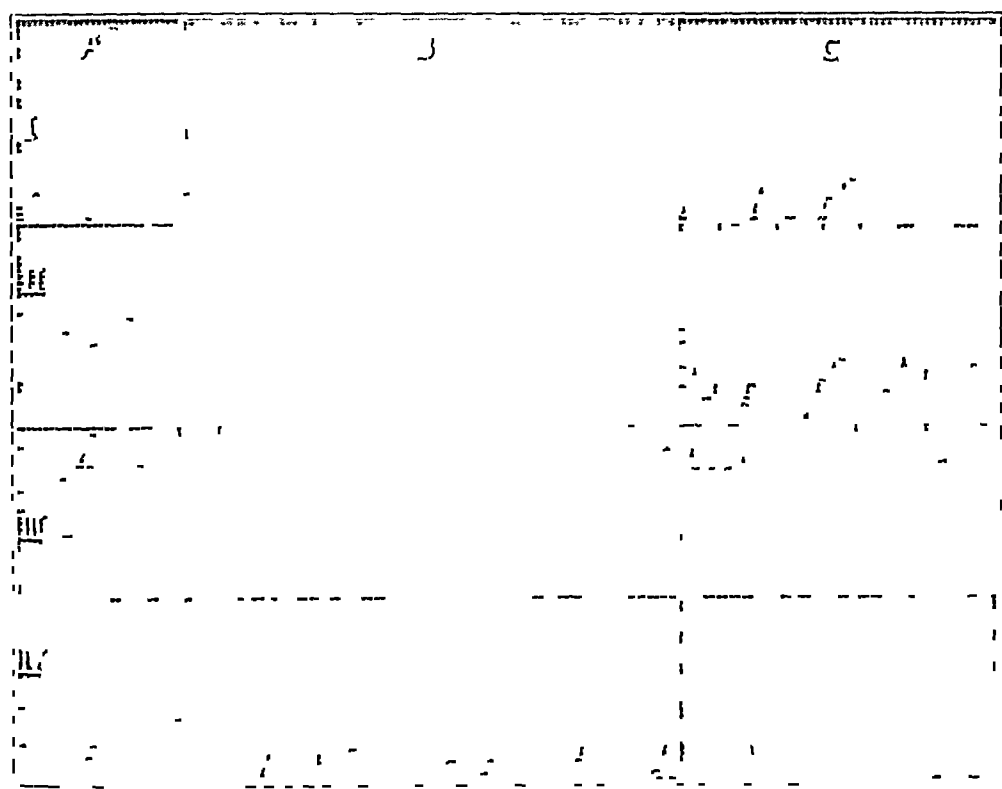


Fig 1 (case 1)—Electrocardiograms *A*, two years before admission, regular sinus rhythm, rate 110, marked preponderance of the left ventricle and high voltage of the QRS complex. The T wave is deeply inverted in leads I and IV and diphasic in lead II. The record is characteristic of enlargement of the left ventricle as seen in cases of long-standing hypertension. *B*, one day after admission, incomplete auriculoventricular dissociation, with frequent dropped beats, auricular rate 150, ventricular rate 100 to 140. The RS-T transition is markedly depressed in leads I, II and IV. The T wave has become diphasic in leads I and II, low in lead III and upright in lead IV. *C*, two days after admission, regular sinus tachycardia, rate 140, with normal auriculoventricular conduction. The depression of the RS-T transition in leads I, II and IV is more marked, there is also a slight depression in lead III.

myocardium. The coronary ostia were normal. The coronary arteries revealed only slight intimal thickening, without encroachment on the lumen and without any occlusions.

Histologic examination of multiple sections of the left ventricle (figs 2 and 3) revealed widely scattered myofibrils which had undergone necrosis, fatty change and vacuolation, with reactive foci of polymorphonuclear leukocytes, small round cells and fibroblasts. There were also foci of edematous connective tissue. Sections of the wall of the right ventricle revealed, in addition to tinctorial changes, such as smudgy eosinophilic staining of the fibrils with loss of striation, necrosis of the myofibrils, fatty change, scattered interstitial polymorphonuclear



Fig 2 (case 1) —Section of the left ventricle ($\times 150$), showing severe myodegeneration and cellular infiltration

leukocytes and proliferation of young, interstitial fibroblasts. Sections of the auricular myocardium showed peculiar tinctorial changes indicating degeneration of the myofibrils.

Comment —This patient, who was known for four years to have severe hypertension and electrocardiographic changes which occur in hypertension, had few or no evidences of heart failure three weeks

before admission, when she suffered hemiplegia. It is highly probable that the venous thrombosis developed during the three weeks of rest in bed which followed this cerebral accident. The embolism of the pulmonary artery probably occurred in the week before admission, during which time severe dyspnea, weakness, vomiting, a fall in blood pressure and irregular cardiac rhythm were present. The development

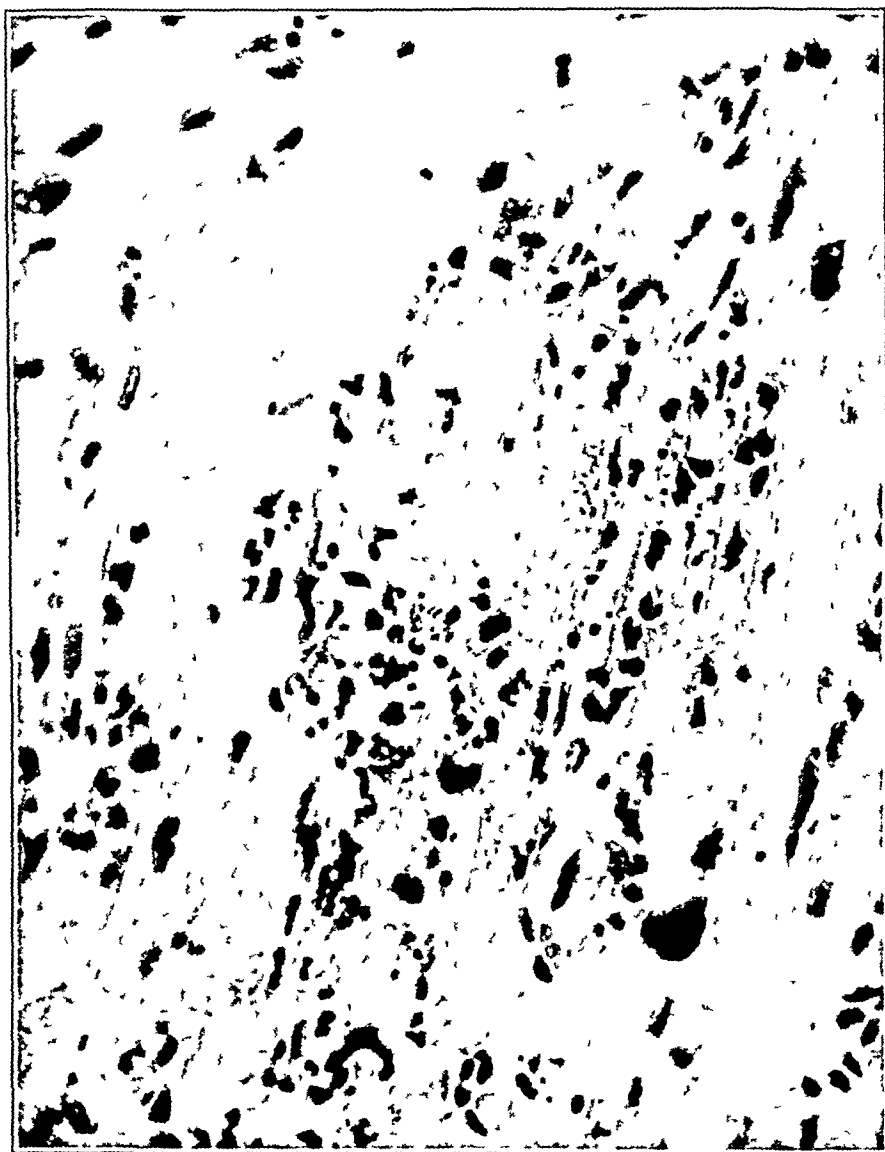


Fig 3 (case 1)—Section of the left ventricle ($\times 400$), showing focal necrosis of the myocardium, with reactive infiltration of polymorphonuclear leukocytes

of a loud, harsh systolic murmur and a systolic thrill and the practical absence of a second sound were undoubtedly due to pulmonary stenosis caused by the extension of the embolus in the pulmonary artery through the pulmonic ring with occlusion of the pulmonary orifice.²² The

22 White and others (footnote 6) Lord⁷ Litten⁸

marked depression of the RS-T transitions and the development of heart block were the consequences of the embolism. The occasional occurrence of heart block in coronary thrombosis and in experimentally induced anoxemia²³ suggests that in this case also it was due to myocardial changes resulting from embolism of the pulmonary arteries. Of interest are the observations of auriculoventricular dissociation by Frommel²⁴ and McGinn and White³ in experimental occlusion of the pulmonary vessels. Histologic studies revealed that the emboli in the present case were in various stages of organization, which indicated that there had been multiple embolization at different times during the past week. The recent distinct myocardial changes, seen both grossly and microscopically, could not be ascribed to organic coronary disease since this was minimal and there was neither narrowing nor occlusion of the coronary vessels.

CASE 2—A man aged 44 had suffered from mild dyspnea on exertion for one year and increasing dyspnea and orthopnea for two or three months. He had also had substernal burning on walking against the wind. Three weeks before admission, while he was walking on the street, sudden severe pain developed in the right scapular region, which was aggravated by respiration and cough. He became dyspneic, so that he had to go to bed, but the symptoms all subsided in one hour. The next day the symptoms recurred for two and one-half hours and were followed by a cough and bloody expectoration.

On examination the patient was found to be dyspneic and orthopneic. There was dulness to flatness at the base of the right lung posteriorly, where diminished breath sounds and fine moist rales were heard. The heart was enlarged to the right and left, the heart sounds were of good quality, and there was a short rough systolic murmur at the base of the heart. The second aortic sound was louder than the second pulmonic. The blood pressure was 140 mm of mercury systolic and 80 mm diastolic. The liver was not palpable. There was edema of both feet. The venous pressure was 4.5 cm of water, the saccharin circulation time twenty-two seconds, the vital capacity 1,100 cc, the temperature 101 F and the white blood cell count 15,600 per cubic millimeter.

The clinical diagnosis on admission was coronary sclerosis, congestive heart failure and pulmonary infarction. Fluid developed at the bases of both lungs. The venous pressure remained the same, and the circulation time became normal. A teleroentgenogram of the chest showed slight enlargement of the left ventricle, elevation of the diaphragm, thickened pleurae, a small pleural effusion on the left and infiltration of the lower lobe of the left lung. An electrocardiogram (fig 4) revealed left axis deviation, a large Q₃, a large S₁ and deep inversion of T₃. The QRS complex was M shaped in lead II. Ten days after admission precordial oppression and air hunger, restlessness and cyanosis suddenly developed. The patient's heart sounds became feeble, and he died fifteen minutes later.

23 Resnik, W. H. Observations on the Effect of Anoxemia on the Heart I. Auriculo-Ventricular Conduction, *J Clin Investigation* 2:93, 1925. Lewis and Mathison¹²

24 Frommel, E. Les troubles du rythme cardiaque au cours de l'embolie pulmonaire, *J de physiol et de path gen* 26:247, 1928.

The postmortem diagnosis was multiple emboli of the pulmonary artery and its branches, multiple infarcts of the lower lobe of the right lung, sclerosis of the coronary arteries with narrowing, especially of the right circumflex artery, myofibrosis of the posterior wall of the left ventricle, hypertrophy of the left ventricle, and nephrosclerosis. The site of origin of the embolus could not be ascertained, because the incision at autopsy was limited.

The heart weighed 350 Gm. The right auricle was slightly dilated and contained within its lumen two free, grayish red, granular, friable masses. The right ventricular chamber was moderately dilated and contained coiled embolic masses

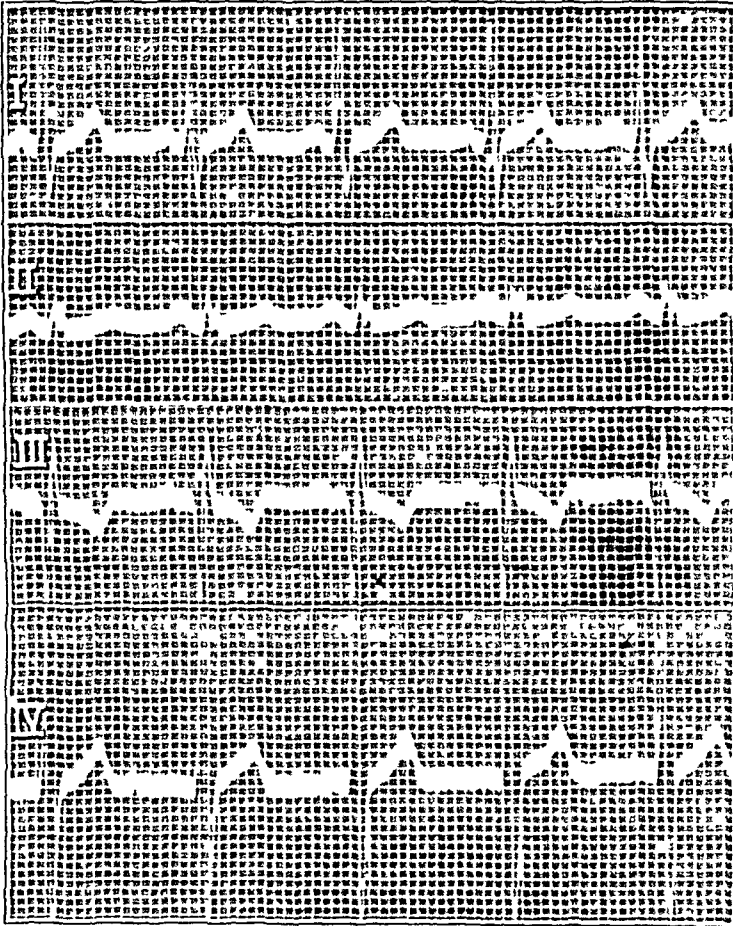


Fig 4 (case 2) —Electrocardiogram made on admission, regular sinus rhythm, rate 90, deviation of the axis to the left. There are a deep S_1 and a deep Q. The QRS complex is M shaped in lead II. T is inverted. The record is suggestive of either posterior myocardial infarction or embolism of the pulmonary artery.

similar to those in the right auricle. The lumen of the left main trunk of the pulmonary artery contained a granular, bloodlike, cylindric body, which extended into the right main branch and the branch to the lower lobe of the right lung and occluded the latter. The embolus in the main right pulmonary artery had become adherent to the intimal surface. The myocardium of the posterior wall of the left ventricle showed an extensive, stellate, gray-white, firm, fibrous zone. The coronary ostia were patent. There was widespread sclerosis of the coronary arteries, especially of the right, with moderate narrowing of the lumens.

Histologic examination of various portions of the left ventricle revealed focal areas of myomalacia, with subendocardial hemorrhage, vacuolar degeneration of the myofibrils, scattered proliferation of mesenchymal cells and occasional wide zones of interstitial polymorphonuclear leukocytes. There was also evidence of patchy fibrosis and a moderate degree of fatty change. Sections through the right ventricle showed evidence of myodegeneration, with an occasional polymorphonuclear leukocytic reaction.

Comment—This patient had apparently suffered from mild anginal symptoms and recent slight failure of the left side of the heart probably due to an organized myocardial infarct. The swelling of the right ankle three weeks before admission may have indicated the occurrence of thrombophlebitis of the right leg, from which subsequent embolization of the pulmonary artery occurred. Undoubtedly the first embolism took place three days before admission, when the patient had the sharp thoracic pain and dyspnea, while the hemoptysis on the day before admission must be considered indicative of pulmonary infarction. There had been mild symptoms of failure of the left side of the heart for three months, but they had disappeared shortly after admission, at which time the circulation time and venous pressure were normal. During the ten subsequent days, before final embolism caused death, there was evidence neither of cardiac failure nor of shock. The electrocardiogram made on admission showed the changes which are accepted as common in cases of embolism of the pulmonary artery but which might more probably have been due to an organized infarct of the posterior wall of the left ventricle. Post mortem examination revealed acute myocardial changes which could not be accounted for by any recent coronary occlusion.

CASE 3—A housewife aged 58 had suffered from bleeding hemorrhoids for many years. Four and a half months before admission pain developed in the left upper quadrant of the abdomen, associated with slight fever. Five days before admission there were symptoms of intestinal obstruction. Except for abdominal distention and the presence of external and internal hemorrhoids, the physical examination showed no abnormality. The size and sounds of the heart were normal. The blood pressure was 140 mm of mercury systolic and 80 mm diastolic.

With the patient under spinal anesthesia, a cecostomy was performed for carcinoma of the descending colon. The patient's convalescence was uneventful until the eighth day after operation, when she suddenly went into coma and became pale and slightly cyanotic. Her respirations were stertorous and rapid. She died ten minutes later.

The postmortem diagnosis was massive recurrent embolism of the pulmonary artery, carcinomas of the descending and sigmoid colon, with hepatic and mesenteric metastases, localized fibrinous peritonitis at the site of cecostomy, hypertrophy of the heart, pulmonary congestion and edema, hydrothorax on the left side, dilatation of the right auricle and ventricle, and coronary sclerosis without narrowing. Permission for necropsy did not allow a peripheral search for the origin of the thrombus.

The heart weighed 465 Gm. The right auricle was considerably dilated. The right ventricle was moderately dilated, and its trabeculae carneae were considerably flattened. Within the right ventricular chamber and extending into the pulmonary artery were several portions of an inelastic, grayish red blood clot, approximately 7 cm in length and 1.5 cm in width. This clot extended also into the medium-sized ramifications of the pulmonary artery. The coronary ostia and vessels were widely patent throughout. Their walls showed only a moderate number of flat, intimal arteriosclerotic plaques.

Histologic examination of the septum revealed scattered foci of fatty change and glycogen. There were several localized areas of necrosis, with early cellular response of polymorphonuclear leukocytes and lymphocytes. These foci were situated chiefly in the subendocardial zones. There were also patches of edematous and young (cellular) connective tissue. Within the right ventricle were slightly patchy cellular zones of connective tissue.

Comment—In this case the previous history was not suggestive of cardiac disease. Evidence of massive embolism of the pulmonary artery first appeared on the eighth day after an operation, possibly from a thrombus in the veins of the lower extremities. The appearance of the lungs suggested repeated embolization. Death occurred within ten minutes after the onset of collapse. Acute microscopic cardiac damage was observed, without any noteworthy concomitant coronary disease.

CASE 4—An actress aged 75, who had had rheumatic fever in childhood and had known that she had valvular heart disease for at least twenty years, had been free from symptoms until four years before admission, when dyspnea and precordial pain developed on exertion. Two weeks before admission, while rehearsing in a play, she became markedly dyspneic when at rest and orthopneic. Six days before admission she had a sharp attack of dyspnea and substernal pressure, which radiated to the back. These symptoms increased until she was admitted to the hospital.

Examination revealed an orthopneic and dyspneic woman in severe shock, with marked pallor of the skin and cyanosis of the extremities, especially of the nail beds. The respiratory rate was 36 and the pulse rate 124, per minute. The skin was cold and moist, and the veins of the neck were full, but those of the extremities were collapsed. The heart was enlarged to the left, and the heart sounds were of poor quality. The second aortic sound was louder than the second pulmonic. The blood pressure was 95 mm of mercury systolic and 60 mm diastolic. Respiratory sounds were diminished, with dulness and rales at the bases of both lungs, especially on the left. Slight edema of the ankles and sacral region was noted. Pulsation of the dorsalis pedis arteries was absent.

The clinical diagnosis was multiple occlusions of the coronary arteries, with recent embolization of the pulmonary artery. Despite various therapeutic measures, the patient died several hours after admission.

The postmortem diagnosis was multiple recent pulmonary infarcts, with multiple emboli in the arteries of all lobes of the lungs, coronary arteriosclerosis, with extreme narrowing of the right circumflex artery, myocardial fibrosis, especially of the posterior wall, with aneurysmal dilatation, mural thrombus of the left ventricle, and bilateral hydrothorax.

The heart weighed 400 Gm. The right ventricle was slightly hypertrophied and its chamber somewhat dilated. The interventricular septum bulged considerably into

the lumen of the right ventricle. The endocardium over the posterior wall of the left auricle showed slight, irregular wrinkling. There was diffuse thickening of the mitral leaflets and of their associated chordae tendineae. An aneurysmal dilatation of the left ventricle was observed near its apex. There were several grayish red masses adherent to the left ventricular endocardium and embedded among the trabeculae carneae. Section of the myocardium in this region showed diffuse grayish white streaking and fine yellowish tigering. The coronary ostia were patent. There was moderate thickening of the coronary arteries, with scattered zones of severe narrowing but no evidence of recent occlusion. Within the branch of the pulmonary artery to the upper lobe of the right lung was a friable gray-white embolus, approximately 10 cm in length, partially occluding the lumen. Section of the lobes of the lung disclosed many grayish red embolic masses projecting from the mouths of the small branches of the pulmonary artery.

Histologic examination of sections of the anterior and septal portions of the left ventricle showed focal zones of necrosis with polymorphonuclear leukocytic reaction, severe vacuolar degeneration of the muscle and distinct tinctorial changes. There were also widespread foci of interstitial hemorrhage. The right ventricle showed focal hemorrhage and fibrosis, with only moderate fat. The posterior wall of the left ventricle showed only slight fatty change.

Comment—This patient, with rheumatic heart disease, had suffered from symptoms of cardiac failure and precordial pain for four years. These can be attributed to the old myocardial infarct and ventricular aneurysm observed at postmortem examination. Embolism of the pulmonary artery began one or two weeks before admission and was probably secondary to peripheral venous thrombosis. While the emboli did not occlude the main pulmonary artery, as in the previous cases, there were numerous emboli in the smaller branches, so that much of the pulmonary bed was obstructed. Although there was definite disease of the coronary arteries with marked narrowing, there were no recent occlusions to explain the recent myocardial necrosis.

COMMENT

In the 4 cases presented, microscopic study of the myocardium revealed significant acute damage of the type usually seen in cases of recent coronary occlusion. In 4 other cases, of a similar but distinctly less pronounced condition, more localized myocardial alterations were observed. In 2 cases (1 and 4) recent myocardial damage was suspected on macroscopic examination because of a yellowish brown mottling of the subendocardial myocardium, associated with fine gray perivascular streaking. Other gross changes of the myocardium could be ascribed to fibrosis due to previous coronary occlusion, such as occurred in 2 instances. The microscopic alterations varied in severity and extent from tinctorial changes, loss of striation, fatty change and vacuolation of fibers to focal areas of necrosis, with reactive foci of polymorphonuclear leukocytes, round cells and, finally, fibroblasts. These changes were more predominant in the subendocardial region. In 3 instances

these acute alterations affected both ventricles as well as the interventricular septum. The left ventricle, however, was much more frequently, and usually more extensively, affected. We have not sufficient data to state whether the posterior or the anterior wall of the left ventricle was more severely damaged. Generally the ischemic changes were seen in both walls. In addition, the intensity of the damage was difficult to evaluate because of the association of fibrotic zones in some of the cases.

An attempt was made to determine the factors which led to the development of acute myocardial damage in some cases of embolism of the pulmonary artery and not in others. In one group of 29 cases which were studied there was evidence of recurrent embolization, and death occurred days or weeks after the first embolism. In a second group of 13 cases there was a single embolus in the pulmonary artery with sudden death within a few hours or minutes. All cases of acute myocardial damage fell into the first group. This indicates that the duration of life after embolization is an important factor in the development of myocardial change. Apparently such damage did not develop unless days or weeks elapsed after the initial embolus.

The cases in which acute myocardial damage occurred and those in which it did not were compared with regard to the severity of coronary atherosclerosis and narrowing. In the latter group the coronary arteries showed relatively little or no sclerosis and no narrowing except in 2 cases, in which it was slight. On the other hand, in the group comprising cases of embolism of the pulmonary artery with acute myocardial damage the coronary arteries usually showed widespread sclerosis and narrowing. In 5 of the 8 cases of acute myocardial damage there was moderate to extreme narrowing of the lumen of one or more major branches of the coronary arteries. In 2 of these there were severe sclerotic narrowing of the coronary arteries and old myocardial infarction. However, in 3 of the cases of acute myocardial damage there was no significant narrowing of the coronary vessels. Distinct areas of grossly visible myomalacia occurred in the cases in which the most intense narrowing of the coronary arteries was observed. In 2 instances of grossly visible change, however, the lumens of the coronary arteries were normal in caliber but the heart was distinctly hypertrophied. From these data it appears that acute myocardial damage occurs most frequently in association with narrowing of the coronary arteries but that such damage may also occur although less frequently, when the coronary arteries show no significant anatomic alteration, provided the heart is hypertrophied.

The weights of the hearts which showed acute myocardial damage were compared with the weights of those which did not. While there were distinct variations in each group with few exceptions the hearts

with acute myocardial damage were considerably hypertrophied, while those without such damage were relatively normal. The average weight of the heart in the first group was 390 Gm and that in the second group was 357 Gm. These averages are partly misleading, because in the first group the heart in 1 or 2 cases weighed less than 350 Gm, but belonged to a cachectic person and might have been regarded as hypertrophied if the cardiac weight had been considered in terms of low body weight. On the other hand, the weight of the heart in 1 case in the second group was recorded as 580 Gm, but the heart itself was not available for study, and only a few routine sections of the myocardium could be examined histologically. With these possible exceptions, it appeared that acute myocardial changes occur much more readily in hypertrophied hearts than in those of normal size. In summary, then, acute alterations following recurrent embolism of the pulmonary artery were favored by three factors: (1) duration of life from several hours to one or more weeks after the initial embolus, (2) preexisting coronary arteriosclerosis with narrowing and (3) hypertrophy of the heart.

The chronologic relation between embolism of the pulmonary artery and the acute myocardial damage cannot be determined with certainty. Any conclusion that the embolism played a role in the production of the myocardial changes would necessarily presuppose proof that the embolism occurred before the development of the myocardial change. That this relation actually existed in the cases described can be inferred only indirectly. Consideration of the clinical history indicates that the first pulmonary accident generally occurred a week or more prior to the death of the patient. It is probable, at least, that in some of the cases the first embolism occurred three or more weeks before death, because there was a rapid fall in blood pressure at that time which could not be explained by any factor other than the embolism. While the age of the myocardial lesion cannot be definitely determined, the changes in some of the areas give the impression of being recent, and probably of only a few days' duration. The chief reason for believing that the embolism preceded the acute myocardial changes is the absence of any other factor which could reasonably account for the production of such myocardial injury. In 2 cases in which the condition occurred there was evidence of an old coronary occlusion (marked arterial narrowing) with a corresponding old, healed infarct. But neither in these nor in any of the other cases in which myocardial damage was noted was there any evidence, on detailed examination, of a recent coronary obstruction such as might be expected to produce the acute myocardial changes which we observed.

Finally, one must consider the possible role of cardiac failure in causing these myocardial changes. There was a significant degree of heart failure in 3 of the 8 cases presented. In each of these there was severe narrowing of the coronary arteries with myofibrosis which prob-

ably precipitated the failure. Whether myocardial failure with its attendant disturbances in circulatory dynamics is capable of producing acute myocardial damage is uncertain. In these 3 cases it would be difficult to understand why failure of several months' or years' duration should suddenly precipitate acute myocardial damage. The only reason this possibility is entertained is the observation in other studies which we have made on coronary insufficiency, that, under special circumstances, cardiac failure may play a role in the production or exaggeration of acute myocardial damage. In the present series, however, the absence of cardiac failure in 5 of the 8 cases in which the condition was seen clearly indicates that some other factor must be invoked to explain the recent damage to the muscle.

The theoretic cause of death and basis for the occurrence of cardiac sequelae in embolism of the pulmonary artery have been discussed. In the cases which we studied, the embolism caused a sufficient degree of obstruction of the pulmonary vascular bed to be a factor in the production of profound shock and of death. In some of the cases the main pulmonary artery was practically completely occluded, while in others so many of the major branches were obstructed that an equivalent amount of interference with the pulmonary circulation must have existed.

Despite the extent of obstruction of the pulmonary circulation, significant dilatation of the right side of the heart was not invariably present. A marked degree of dilatation was observed in only 2 of the cases of recurrent embolism of the pulmonary artery and in only 2 of the 13 cases in which death followed a single embolus. Moderate or slight dilatation of the right ventricle was encountered in many of the cases, but it should be emphasized that the evaluation of such lesser degrees of dilatation at postmortem examination is fraught with difficulties and is therefore uncertain. Furthermore, except for the 2 instances of severe dilatation of the right ventricle after a single fatal embolus of the pulmonary artery, other factors, such as failure of the left side of the heart, may have been responsible. The infrequency of dilatation of the right ventricle may be explained in some cases by the rapidity with which death ensued and in others by the intense shock following extreme obstruction of the pulmonary circulation and diminution of blood volume returning from the periphery to the right ventricle. In 1 of our cases a loud systolic murmur and a systolic thrill gave evidence of obstruction of the pulmonary artery—signs already pointed out by Litten.⁸ Special reference to the second pulmonic sound was not found in the records of these patients. In 1 case it was observed that there was an elevation of pressure in the cervical veins without a similar rise in the peripheral veins. This may not necessarily be interpreted as indicating failure of the right side of the heart because in the

presence of shock, with its peripheral vasoconstriction, there may have been a redistribution of blood from the periphery to the cerebral vessels, with relative increase in venous return from the latter and diminution from the former ²⁵

The explanation for the anatomic myocardial changes observed in our cases appears to lie in the development of ischemia of the myocardium. Of the theoretic causative factors discussed earlier, neither pulmonary-coronary vagal reflexes nor generalized anoxemia can be invoked. That constriction induced by vagal stimulation could occur in severely sclerotic coronary arteries seems anatomically unlikely. Shock with a concomitant drop in systemic, and therefore in aortic, blood pressure was probably the dominant factor in the production of myocardial ischemia and of the acute myocardial injuries which we have described. Marked degrees of shock and diminution in blood pressure were present in all the cases in which anatomic examination disclosed acute myocardial damage. Furthermore, electrocardiographic changes when present always followed the onset of clinical shock with diminution in blood pressure.

The explanation for the occurrence of acute myocardial damage in some cases and not in others has already been attempted. Apparently the myocardial ischemia induced by diminished aortic pressure was inadequate unless other favorable elements were present. Thus we believe that when the myocardium was already suffering from previous coronary disease with narrowing or old occlusion sufficient to cause relative ischemia, or when the heart was large with an abnormally great demand for blood, or particularly when with these combined factors recurrent embolism of the pulmonary artery reduced the blood pressure over a sufficiently long period, the degree of ischemia became adequate actually to produce its morphologic expression. Then, even in the absence of a recent coronary occlusion, coronary insufficiency was precipitated by the fall in aortic pressure adequate to induce acute myocardial damage, which in some instances was similar in severity to that observed in cases of actual coronary occlusion ²⁶. Support for this concept is found in our observation, which is the subject of another report, ²⁷ of similar acute myocardial damage in the absence of acute coronary occlusion in conditions other than embolism of the pulmonary artery, in which shock coexisted with coronary disease. In cases of

25 Fishberg, A. M. Redistribution of Blood in Heart Failure, *J. Clin. Investigation* **17** 510, 1938.

26 Buchner, F., Weber, A., and Haager, B. Koronarinfarkt und Koronarinsuffizienz in vergleichender elektrokardiographischer und morphologischer Untersuchung, Leipzig, Georg Thieme, 1935.

27 Friedberg, C. K., and Horn, H. Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J. A. M. A.* **112** 1675 (April 29) 1939.

severe shock lasting several days such organic damage may be produced even though there is no significant coronary disease, as seen in our first case

In view of the anatomic changes which we have described, it appears that the typical electrocardiographic alterations observed in cases of embolism of the pulmonary artery, which so closely simulate those of myocardial infarction, could be explained on the basis of myocardial ischemia. However, electrocardiographic changes typical of embolism of the pulmonary artery, such as depression of the RS-T transition in lead I and elevation in lead III, inversion of T_2 and T_3 and a large Q_3 , also were observed in some of the cases in which no anatomic changes were seen in the myocardium. But even in these cases it appeared fair to assume that myocardial ischemia was present, even though it was not of sufficient severity or duration to result in organic alteration of the heart muscle. That temporary coronary insufficiency can induce such functional changes in the myocardium is shown by the acute transient electrocardiographic changes observed in patients during an attack of angina pectoris due to disease of the coronary arteries. These patients may return to their previous functional status with complete and rapid regression of the objective and subjective phenomena, after removal of the factor which has produced coronary insufficiency.

Some of the electrocardiographic changes found in cases of embolism of the pulmonary artery, such as the tendency to right axis deviation and the development of a large S_1 wave, probably represent strain on the right ventricle. The absence of dilatation of the right ventricle, as seen post mortem or even at operation, does not preclude the existence of increased tension on the pulmonary artery and the right ventricle.²⁸ That strain on the right ventricle and engorgement of the inferior vena cava do exist was indicated by the report of Keschner and Klemperer,²⁸ who showed that hepatic edema is approximately as frequent in cases of embolism of the pulmonary artery as in those of prolonged cardiac failure. Furthermore, the development of these evidences of strain on the right ventricle depends in part on whether the relative size of the cardiac chambers was previously normal or whether there was hypertrophy of the left ventricle associated with hypertension and hypertensive heart disease.

Love and his co-workers²⁹ concluded, as a result of their studies on experimental embolism of the pulmonary artery in dogs, that the elec-

28 Keschner, H. W., and Klemperer, P. Frequency and Significance of Hepatic Edema, *Arch Path* 22: 583 (Nov.) 1936.

29 Love, W. S., Jr., Brugler, G. W., and Winslow, N. Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization, *Ann Int Med* 11: 2109, 1938.

trocardiographic changes observed were due entirely to dilatation of the right ventricle. These findings cannot be applied directly to embolism in man, not only because of the difference in species but because the experiments were of brief duration and the hearts and coronary vessels were normal. In our cases of acute cardiac damage the embolism was recurrent, with several days at least elapsing before death, and the hearts were generally hypertrophied and the coronary arteries narrowed.

The absence or presence of electrocardiographic changes in cases of embolism of the pulmonary artery and their variations in appearance might be explained by variations in the degree of myocardial ischemia and of strain on the right ventricle. The former would depend on the severity and duration of shock, the absence or presence of previous severe coronary disease and the vascular demands of the muscle mass, and the latter, on the absence or presence of previous preponderance of the left ventricle and the cross-sectional area of arterial obstruction.

It is not clear why the electrocardiographic pattern of embolism of the pulmonary artery resembles that of posterior rather than that of anterior myocardial infarction. The only experimental evidence which bears on this point is that of Buchbinder and Katz,³⁰ who observed that after compression of the pulmonary artery the heart revealed epicardial and intramuscular hemorrhages in the basal portion of the ventricles. In our anatomic observations there did not appear to be a preponderance of myocardial damage either at the base of the heart or on the posterior wall. Neither could we observe any evidence that the blood supply of the right coronary artery was more impaired than that of the left. However, the marked rise in intraventricular pressure that must have been present within the right ventricle might have increased the resistance to flow in the right coronary artery³⁰ sufficiently to affect disproportionately those portions of the heart, particularly the posterior wall which are supplied by that vessel.

SUMMARY AND CONCLUSIONS

A group of 42 cases of embolism of the pulmonary artery has been studied, in 8 of which recent structural changes in the myocardium ordinarily resulting from acute myocardial ischemia were revealed.

The factors necessary for the production of such myocardial changes are discussed. These are shock, asphyxia and exaggerated vagal reflexes resulting from obstruction of the pulmonary arteries. These factors, alone or in association, lead to insufficiency of the coronary circulation.

30 Gregg, D. E. Phasic Blood Flow and Its Determinants in the Right Coronary Artery, *Am J Physiol* **119** 580, 1937.

Morphologic evidence of coronary insufficiency in cases of embolism of the pulmonary artery is more likely to occur if there are recurrent embolization, narrowing of the coronary arteries, cardiac hypertrophy and adequate duration of life after embolism.

Anatomic changes in the myocardium in persons with embolism of the pulmonary artery may be considered the end result of the myocardial ischemia which accounts for the characteristic electrocardiographic changes.

The resemblance of electrocardiographic changes in cases of embolism of the pulmonary artery to those in cases of myocardial infarction of the posterior wall may be explained by the diminished flow through the right coronary artery resulting from increased tension in the right ventricle.

CALCIUM AND DIGITALIS SYNERGISM

THE TOXICITY OF CALCIUM SALTS INJECTED INTRAVENOUSLY
INTO DIGITALIZED ANIMALS

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Certain similarities in the action of the glucosides of the digitalis group and of calcium on the heart have led to the hypothesis that they may be related in their action¹ There is no general agreement as to the character of this relation Some investigators have maintained that

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1 (a) Billigheimer, E Ueber Wirkung und Zusammenhange von Calcium und Digitalis, *Klin Wchnschr* **8** 724-726 (April 16) 1929 (b) Bower, J O, and Mengle, H A K The Additive Effect of Calcium and Digitalis A Warning, with a Report of Two Deaths, *J A M A* **106** 1151-1153 (April 4) 1936 (c) Fischer, H Beitrag zur Frage des Synergismus zwischen Digitalis- und Calciumwirkung, *Arch f exper Path u Pharmakol* **130** 194-241, 1928 (d) Gold, H, and Edwards, D J The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, *Am Heart J* **3** 45-50 (Oct) 1927 (e) Gold, H, and Kwit, N Digitalis and Calcium Synergism, *Science* **86** 330-331 (Oct 8) 1937 (f) Goldberg, S J The Use of Calcium Gluconate as a Circulation Time Test, *Am J M Sc* **192** 36-41 (July) 1936 (g) Golden, J S, and Brams, W A Mechanism of the Toxic Effects from the Combined Use of Calcium and Digitalis, *Ann Int Med* **11** 1084-1088 (Jan) 1938 (h) Lieberman, A L Studies on Calcium VI Some Inter-Relationships of the Cardiac Activities of Calcium Gluconate and Scillaren-B, *J Pharmacol & Exper Therap* **47** 183-192 (Feb) 1933 (i) Loewi, O Ueber den Zusammenhang zwischen Digitalis- und Kalziumwirkung, *Arch f exper Path u Pharmakol* **82** 131-158 (Dec 20) 1917 (j) Mandelstamm, M Ueber den Zusammenhang zwischen Digitalis- und Calciumwirkung, *Ztschr f d ges exper Med* **51** 633-651, 1926 (k) McGuigan, R A, and Higgins, J A The Influence of Calcium Salts on Digitalis Action, *J Lab & Clin Med* **23** 839-844 (May) 1938 (l) Wolffe, J B, and Bellet, S Cessation of Attacks of Auricular Paroxysmal Tachycardia by the Use of Calcium, *Ann Int Med* **4** 795-803 (Jan) 1931

their effects are partially or completely additive,² others, that they are truly synergistic,³ in other words, the effects resulting when they are given together exceed the effects to be expected from the sum of their individual actions. The term potentiation is at times used in a sense equivalent to that of synergism.

The experiments presented here are concerned with the effects on the previously digitalized animal of calcium salts injected intravenously. This particular problem has evident special importance in clinical medicine.

PROCEDURE AND RESULTS

Effects of Calcium Alone—The effects on the heart of calcium salts injected intravenously into dogs have been reported in detail elsewhere.⁴ Serial electrocardiograms were taken during the course of continuous intravenous infusion of an isotonic solution of calcium chloride, and the sequence of changes up to the time of the death of the dogs was observed. By determining the concentration of calcium in samples of blood serum taken at intervals during the infusion, it was possible by interpolation to establish the concentration of calcium associated with each change in the electrocardiographic sequence.

A phase of inhibition appeared first, manifested by slowing and all degrees of auriculoventricular block. This occurred at concentrations of calcium of 15 to 40 mg per hundred cubic centimeters. At slightly higher levels, 30 to 65 mg of calcium per hundred cubic centimeters, a phase of enhanced automaticity developed, associated with extrasystoles and tachycardia and culminating in ventricular fibrillation and death in half of the experiments. In the animals in which ventricular fibrillation did not develop, this period of enhanced automaticity was replaced by a second slowing phase, terminating in cardiac arrest at concentrations of calcium in the serum of 79 to 190 mg per hundred cubic centimeters.

The mode of death could not be correlated with the rate of injection. Death by arrest occurred at higher levels of calcium in the serum and so required larger doses of calcium than death by fibrillation, but this is merely an expression of the fact that the animals dying by arrest survived the period of increased automaticity. It gives no clue to the reasons for the death of some and the survival of others beyond this period. Death occurred in some cases after the administration of as little as one tenth of the dose of calcium required to kill others. The

² Lieberman^{1b}, Mandelstamm^{1c}, McGuigan and Higgins^{1d}

³ Billigheimer^{1a}, Fischer^{1c}, Gold and Edwards^{1d}, Gold and Kunit^{1e}, Golden and Brans^{1g}

⁴ Hoff, H. E., Smith, P. K. and Winkler, A. W. Electrocardiographic Changes and Concentration of Calcium in Serum Following Intravenous Injection of Calcium Chloride. *Am J Physiol* **125**: 162-171, 1939.

great variations in the levels of calcium in the serum at which death occurred and in the doses required to kill make it difficult to speak with any accuracy of a lethal dose of calcium

Effects of Digitalis Alone—Digitalis is now usually standardized by the intravenous injection of the drug in divided doses every few minutes until the animal succumbs⁵ The acute fatal dose as determined by this divided dose method, although it yields consistent results, is necessarily higher than that determined by any single dose method, as the portions injected in the last intervals will not have had time to exert their full effects before death occurs The most recent determinations of the acute fatal dose of digitalis in dogs has been made by McGuigan⁶ and by McGuigan and Higgins,¹¹ the average amount according to their experiments being 1.0 to 1.2 cc of the tincture per kilogram of body weight

In the experiments reported in this paper a tincture was freshly prepared from standardized leaves and adjusted to the U S P standard In order to determine its potency, the diluted tincture was injected intravenously into 6 normal dogs, the dose being 0.6 cc per kilogram, or one-half the expected acute fatal dose as determined by the divided dose method Three of the animals died one to six hours later, with the typical contracted heart of digitalis poisoning The other 3 survived This demonstrates the approximate identity of half the acute fatal dose as determined by McGuigan and the 50 per cent lethal dose as usually determined for most drugs The latter is defined as that dose which will produce death in half the animals studied without consideration of time of death These experiments serve to define pharmacologically the dose of digitalis used in our later combined experiments and indicate the expected toxic result if digitalis were to be given alone without calcium

Effects of Calcium on the Digitalized Heart—Twelve dogs under morphine analgesia were given 0.6 cc of well diluted tincture of digitalis per kilogram of body weight One hour later, electrocardiograms of all the animals showed a typical digitalis effect on the heart, with changes in the T wave and ectopic arrhythmias Calcium chloride was then administered exactly as in the case of nondigitalized dogs during which samples of blood were taken periodically and serial electrocardiograms recorded from lead II The results obtained are summarized in table 1 Chart 1 is a schematic representation of the electrocardiographic changes

5 Sollmann, T A Manual of Pharmacology, Philadelphia, W B Saunders Company, 1936

6 McGuigan, R A Pressor and Other Effects of Antipyretics on Digitalis Action, Proc Soc Exper Biol & Med **38** 314-315 (April) 1938

The effect of the injection of calcium was indistinguishable from its influence on the normal heart. The phase of inhibition was first to appear and it effectively suppressed the ectopic beats and arrhythmias of the digitalized heart. After this the phase of increased automaticity appeared, during which 3 of the 12 animals died suddenly of ventricular fibrillation. The 9 other animals survived the period of hyperexcitability of the heart and succumbed eventually to cardiac arrest. The hearts of

TABLE 1—*Protocols of Experiments*

Experiment No	Weight of Dog, kg	Injections		Specimen of Serum		Mode of Death
		Cc 0.205 Molar Solution of Calcium Chloride	Cc per kg per min	Time, Min	Calcium, Mg per 100 Cc	
1	7.5	28	0.35	10.5	10.2 41.4	Arrest
2	4.7	50	0.38	20.5 27.0	11.0 49.4 71.4	Arrest
3	10.0	130	0.45	10.0 27.5	11.2 50.2 77.6	Arrest
4	6.6	92	0.49	16.0 27.0	11.0 51.4 72.4	Arrest
5	7.1	155	0.50	11.0 37.0 53.0	11.4 31.4 51.4 122.4	Arrest
6	5.4	47	0.92	9.5	11.0 69.4	Arrest
7	6.0	25	1.05	4.0	10.0 33.4	Fibrillation
8	7.2	76	1.10	9.5	10.8 111.6	Arrest
9	7.8	20	1.50	17.0	11.0 47.2	Fibrillation
10	4.8	73	1.70	9.0	11.2 135.2	Arrest
11	7.9	185	1.95	12.0	10.0 59.2	Arrest
12	4.7	11	3.50	0.7	11.0 46.6	Fibrillation

these animals were not in contraction typical of digitalis poisoning nor were they completely dilated as were those of the animals that died of fibrillation.

There are certain ranges of concentration of calcium in the serum at which the principal electrocardiographic changes occur. In chart 2 the concentrations at which these changes appear are compared with the concentrations at which similar changes appeared in the electrocardiograms of the control animal. The data for only 10 of the 20 normal dogs used in the earlier study are included here for purposes of comparison since the remainder received preliminary medication other than

NORMAL SERIES
SERUM CALCIUM
MG PER 100 CC

DIGITALIS SERIES
SERUM CALCIUM
MG PER 100 CC

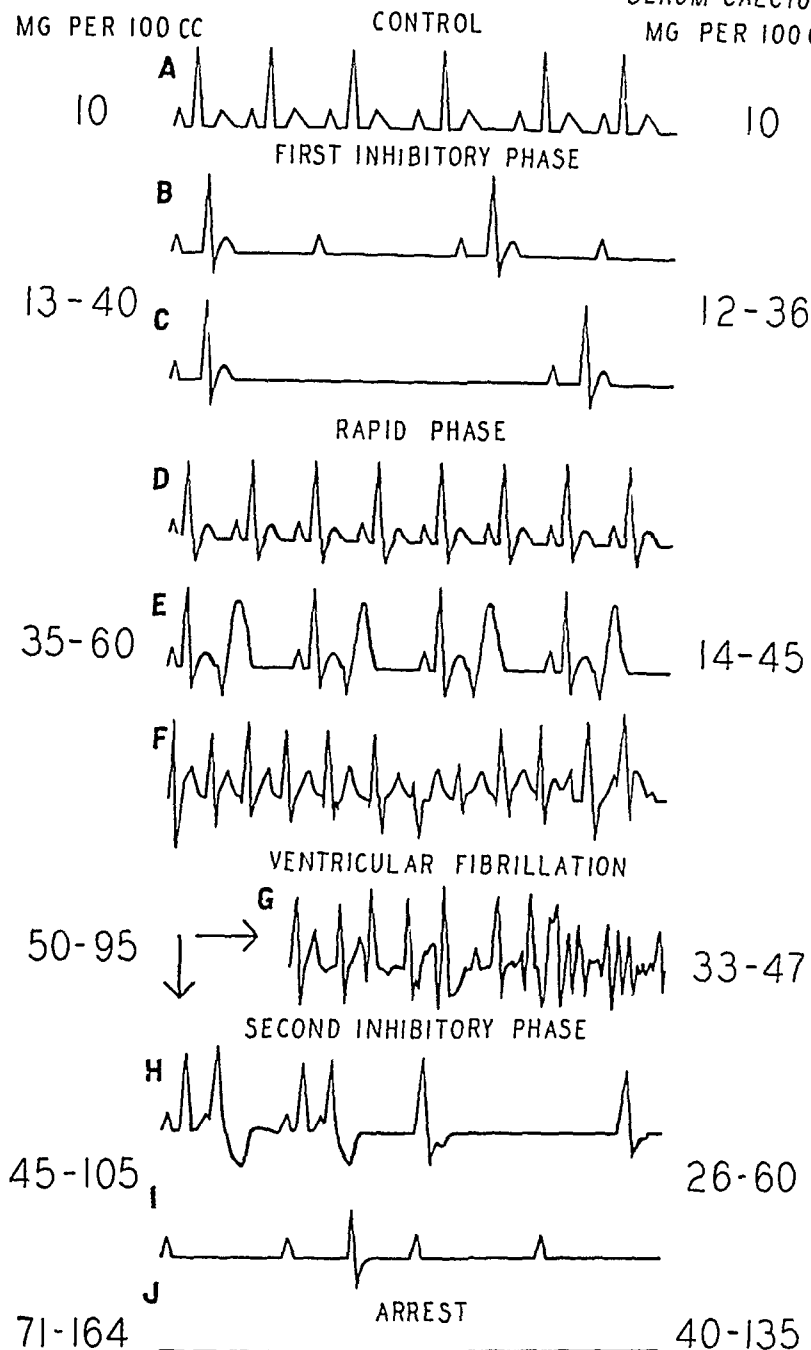


Chart 1—A diagram indicating the electrocardiographic changes produced by the injection of calcium chloride into normal and digitalized dogs. The curves are copies of actual electrocardiograms obtained in a number of experiments. *A*, control dog, showing slight sinus arrhythmia. *B* and *C*, two typical records showing slowing, auriculoventricular delay and block. Changes in the ST interval and the T wave are shown. *D*, *E* and *F* represent the most common events of the rapid phase, namely, a rapid normal rhythm, bigeminy and ventricular tachycardia from various foci. At this point two alternative events occur. The tachycardia may terminate in ventricular fibrillation and death (*G*), or the second slowing phase may intervene (*H*), and the animal will succumb to cardiac arrest (*J*). At the sides are given the extreme ranges of serum calcium values at which the events occurred.

morphine alone. The figures derived from the digitalized animals overlap extensively those from the control series although on the whole they tend to be somewhat lower.

A comparison of the average total amounts of calcium given in each of the two series indicates that there is in this respect no significant difference between them. Such a comparison is however open to the

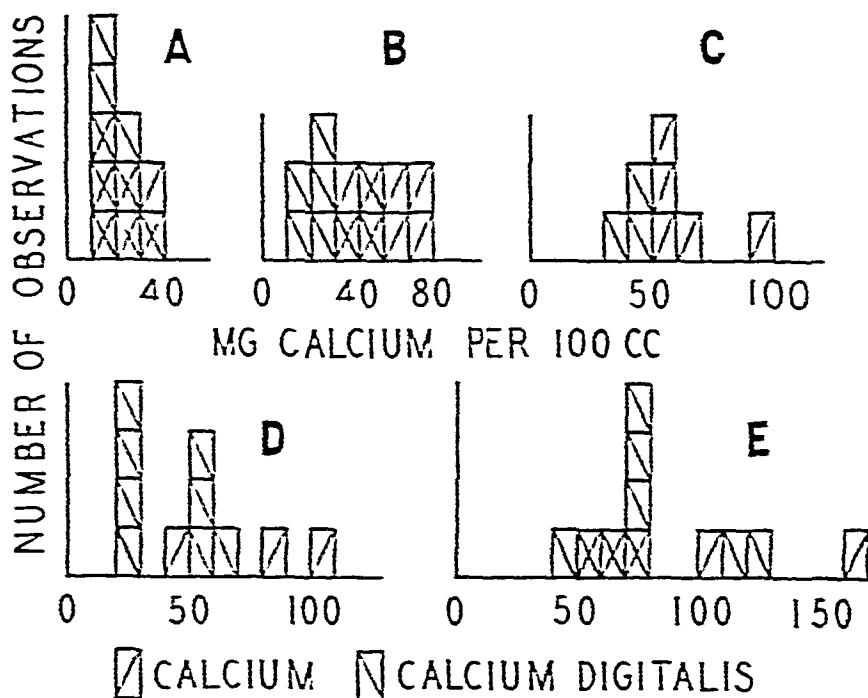


Chart 2—The concentrations of calcium in the serum of normal and digitalized dogs at which typical electrocardiographic changes occur. *A* the first slowing phase; *B* the first rapid phase; *C*, ventricular fibrillation; *D* the second slowing phase; and *E* arrest.

TABLE 2—Concentrations of Ca^{++} in Serum at Death

In Normal Animals, Mg per 100 Cc.	In Digitalized Animals, Mg per 100 Cc.	In Normal Animals, Mg per 100 Cc.	In Digitalized Animals, Mg per 100 Cc.	In Normal Animals, Mg per 100 Cc.	In Digitalized Animals, Mg per 100 Cc.
1.2	1.0	88	1.1	1.2	89
1.1	1.0	21	1.0	1.1	87
1.0	0.9	4	1.0	1.0	47
Mean		93	1.0		73
Probable error of mean				50	74
Significance ratio 0.04					

* This value differs or more than two standard deviations from the mean and may be discarded. If this is done, the new values are mean 74 probable error 60 and significance ratio 0.1.

† The significance ratio is equal to $\frac{D}{PE}$. *D* equals the difference between the two means.

PE equals the probable error and *PE* equals $\sqrt{(\text{PE of one mean})^2 + (\text{PE of the other mean})^2}$. Differences of means are usually considered statistically significant if the significance ratio is greater than 2.0.

objection that the solution was given at varying rates, thus introducing the amount excreted as an undetermined variable. Accordingly the statistical analysis of these figures is not given. A sounder basis of comparison is used in table 2, in which are summarized the concentrations of calcium in the serum in the normal and in the digitalized dogs. The means and the small significance ratios indicate that the concentrations were not significantly lower in the digitalized animals.

COMMENT

There is no evidence from the results presented here that an unusually small dose of calcium will be fatal to the digitalized animal, nor is there evidence that digitalis potentiates calcium by rendering the heart more susceptible to ventricular fibrillation, since 9 animals died in arrest and only 3 from fibrillation.

Evidence for a completely additive action is also lacking. Neither the total quantity of calcium given nor the concentration of calcium in the serum at death was as low as 50 per cent of comparable values for the nondigitalized dogs. The slight reduction in the lethal quantities and concentrations of calcium found here may be indicative of a partially additive effect. Since some partial addition of effects of any two cardiac poisons may reasonably be expected, it is unnecessary to interpret these partially additive results in terms of a specific relation.

It is probable that findings of potentiation reported in the literature are due to two factors: (1) sudden death from ventricular fibrillation produced by calcium at unusually low levels, which occasionally occurs in normal animals, and (2) the fact that half the acute fatal dose of digitalis may kill within an hour or more approximately half the animals to which it is given. The death of such an animal some time after the administration of calcium may be due to the digitalis alone. This may be the explanation of the death in ventricular fibrillation of certain of the animals studied by Golden and Biams,^{1a} who gave 50 to 85 per cent of the acute fatal dose of digalen, and by Bower and Mengle,^{1b} who gave comparable doses. The experiments of Gold and Edwards^{1d} are not directly comparable, since they gave the calcium before giving ouabain.

A lack of additive effect or of potentiation does not, however, mean that the administration of calcium chloride to digitalized patients or to any patients is an entirely safe procedure. Calcium chloride alone, given intravenously to normal animals, is a toxic drug,⁴ its toxicity depending both on the rate of injection and on the total amount given. Its administration to a patient whose failing circulatory system has already occasioned the use of digitalis is probably more dangerous than its administration to other patients, since calcium, like digitalis, has

been shown to produce death by circulatory failure⁴ Our experiments suggest that the danger of injecting calcium into the digitalized patient is simply that of injecting calcium into any patient with cardiac disease and that this in turn probably involves only some intensification of the danger involved in injecting calcium intravenously into a healthy subject Certainly this danger cannot be great in practice, considering the widespread use of calcium intravenously, often no doubt in the presence of cardiac disease⁷

Our experiments indicate that whatever danger is involved in the intravenous use of calcium can be minimized by very slow injection of the salts, so that the local concentration in the heart never attains an unsafe level

SUMMARY

Dilute solution of calcium chloride was administered intravenously to digitalized dogs, and electrocardiograms and samples of blood were taken frequently during the course of the injection

The electrocardiographic changes were correlated with the concentration of calcium in the serum They were similar in every way to those of normal animals receiving calcium

The mode of death of the digitalized animals was by ventricular fibrillation or by arrest without fibrillation, just as in normal animals

A comparison of the fatal dose and of the concentration of calcium in the serum at death in normal and digitalized dogs indicated that, by the type of experiment described here, the lethal effects of calcium and digitalis are neither synergistic nor even completely additive

⁷ Walters, W, and Bowler, J P Pre-Operative Preparation of Patients with Obstructive Jaundice An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, Surg, Gynec & Obst **39** 200-206 (Aug) 1924 Luten, D The Clinical Use of Digitalis, Springfield, Ill, Charles C Thomas, Publisher, 1936 Goldberg¹²

RELATION OF MYASTHENIA GRAVIS TO HYPERTHYROIDISM

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The neuromuscular syndrome named myasthenia gravis has been recognized since its description by Willis¹ in 1685. Since that time many hypotheses have been presented in the literature, but it must be admitted that as yet the essential cause or causes of myasthenia gravis are unknown. This communication is offered as a record of some empiric data concerned with the relation of the uncommon condition myasthenia gravis to the common syndrome of hyperthyroidism. A case is reported in which the two conditions appeared concurrently and in which the one seemed to inhibit or antagonize the other. Observations on a case of myasthenia gravis in which hyperthyroidism was artificially produced are given, together with a review of the literature.

REPORT OF A CASE

M. B., a woman aged 20, was first seen in June 1936. At that time she stated that she had generally been in excellent health until the middle of April, when she saw single objects doubly. This diplopia lasted only a few days and ceased when the left eyelid began to droop. Shortly after this episode she began to tire easily. She became fatigued readily when chewing and swallowing her food. She consulted an ophthalmologist for the visual disturbance and as a result of his advice had a tonsillectomy performed under general (ether) anesthesia. On recovering from this operation she noticed little change in her symptoms except that her facial expression was unaccustomedly blank and her speech at times thick.

Examination at this time revealed an anxious, tired-looking patient with ptosis of the left eyelid. Her gait and station were normal. The cranial nerves showed the following abnormalities: ptosis of the left lid, palsy of the left external rectus muscle, weakness of both superior rectus muscles, weakness of the right external rectus muscle, blank facial expression and rapid tiring of the tongue on repeated movements. There were no sensory disturbances, and the reflex activities were normal. Weakness of the muscles of the extremities was noticed only on prolonged effort.

At this time (June 1936) an ampule of prostigmine (0.5 mg.) was given intramuscularly as a therapeutic test. Within five minutes of the injection the physical signs and symptoms had all but completely disappeared, and the diagnosis

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1 Willis, cited by Guthrie, L. G. Myasthenia Gravis in the Seventeenth Century, *Lancet* 1 330, 1903.

of myasthenia gravis was made. The patient was referred for admission to the Graduate Hospital for further study.

She was admitted to the Graduate Hospital on July 1, to the service of Dr J C Yaskin, at which time physical examination showed some minor changes in the distribution of the extraocular weaknesses. It was noted that her symptoms were at a minimum in the morning and increased as the day wore on. The thyroid gland was slightly enlarged. The degree of weakness was such as to confine her almost constantly to bed. The pulse rate varied from 75 to 120, and the basal metabolic rate was $+19$ per cent. The Wassermann reaction of the blood and of the spinal fluid were negative. The spinal fluid pressure, chemical estimations and cell count were normal. Examination of the blood showed the sugar content to be 93 mg, the urea nitrogen content 10 mg and the cholesterol content 160 mg per hundred cubic centimeters. Roentgenograms of the skull were normal, and there was no roentgen evidence of an enlarged thymus or a substernal thyroid gland.

During the patient's stay in the hospital, aminoacetic acid, benzedrine and acetylbetamethyl choline (mechoyl) were given in physiologic doses. It was not until tablets of prostigmine were given orally that definite and unequivocal improvement was seen. This drug was given in doses of 15 mg three to seven times a day.

The patient continued to lead a fairly normal existence but was dependent on the supply of prostigmine. In February 1937 we prescribed roentgen therapy over the thymic area, but there was no apparent change in the symptoms as measured by the amount of prostigmine necessary. In June 1937, daily injections of 3 cc of thymus extract (Hanson) were given, with the result that the amount of prostigmine needed to control the symptoms was reduced. In September 1937 a control injection of physiologic solution of sodium chloride was substituted for the thymus extract, and the amount of prostigmine used was about one 15 mg tablet two or three times a week, which was considerably less than the patient had heretofore required. At the same time it was noted by both the patient and the examiner that the cardiac rate had increased distressingly and that the neck was swollen. The cardiac rate was frequently observed to be above 200. The basal metabolic rate was now $+52$ per cent, the cholesterol content of the blood was 178 mg per hundred cubic centimeters, and the electrocardiogram showed simple tachycardia of sinus origin. In the presence of these symptoms of thyrotoxicosis it was observed that the myasthenic symptoms had all but vanished. No medication of any kind was given at this time. It was decided to treat the delicately balanced antagonism conservatively, and irradiation therapy over the thyroid gland was begun. After two series of such treatments the basal metabolic rate had retreated to $+30$ per cent and the cardiac rate was measurable at about 140 to 180. After two months a third series of thyroid irradiation treatment was given, and in another two months the basal metabolic rate was $+19$ per cent, the thyroid gland was distinctly smaller and extraocular palsies again became evident. An occasional tablet of prostigmine was then found to be necessary. The pulse rate continued to range between 90 and 130.

COMMENT

It is felt that this case represents a physiologic antagonism between myasthenia gravis on the one hand and hyperthyroidism on the other. At the time of writing the equilibrium established between the two

appears satisfactory from the therapeutic standpoint^{1a} This experience naturally suggested the therapeutic potentiality that artificial hyperthyroidism induced by oral administration of thyroid might be tried in a case of uncomplicated myasthenia gravis Accordingly, a case of myasthenia gravis of moderate severity was selected, and treatment with thyroid given Subjectively and objectively the evidences of myasthenia were reduced, while the pulse rate went to 120 and the basal metabolic rate to +22 per cent (from +5 per cent) The appearance of irritability, excessive perspiration and palpitation in this case indicated that, although the aforementioned antagonism was again evident, there was little therapeutic justification for the continuance of artificial hyperthyroidism

The question arises whether there was not originally some etiologic connection between the therapy directed at the thymus gland and the hyperthyroidism which subsequently appeared The rationale of thymus therapy for myasthenia gravis is predicated on the high incidence of pathologic thymus glands reported to be associated with this condition² There is as yet no certain evidence which will permit the establishment of a thymus-thyroid connection Neither can the possibility of such a connection be wholly excluded It is worthy of note in this connection that Rowntree,³ using the same thymus extract preparation, has in over 100 cases in which various conditions were treated found no instance of hyperthyroidism following its use

The simultaneous occurrence of hyperthyroidism and myasthenia gravis in the same patient seems to be relatively rare, although Buzzard⁴ mentioned it as a common occurrence Of 24 reported cases of hyperthyroidism in which palsy of the extraocular muscles occurred, only 7⁵ appear to be instances of a combination of myasthenia gravis

1a The patient was not seen after Dec 1, 1938 until March 5, 1939, at which time she was sent to the Graduate Hospital She was moribund She had been ill for one week with a grippal infection Huge doses of prostigmine and guanidine failed to prevent death, which occurred in a respirator within six hours of admission

2 Thorner, M W, and Yaskin, J C The Treatment of Myasthenia Gravis, *Am J M Sc* **194** 411, 1937

3 Rowntree, L G Personal communication to the author, 1938

4 Buzzard, F E Myasthenia Gravis, in Allbutt, T C, and Rolleston, H D *System of Medicine*, London, Macmillan & Co, 1910, vol 7, p 51

5 (a) Voss, G Zur Symptomatologie und Therapie der Basedowschen Krankheit, *Deutsche med Wchnschr* **29** 590, 1903 (b) Meyerstein, R Ueber das kombinierte Vorkommen von Myasthenie und Basedowsche Krankheit, *Neurol Centralbl* **23** 1089, 1904 (c) Rennie, G E Exophthalmic Goiter Combined with Myasthenia Gravis, *Rev Neurol & Psychiat* **6** 226, 1908, *M J Australia* **2** 416, 1919, (d) Myasthenia Gravis with Exophthalmic Goiter, *Rev Neurol & Psychiat* **11** 475, 1913 (e) Vedtsmand, H Pluriglandular Insufficiency, *Ugeskr f læger* **85** 405, 1923 (f) Wolff, H G, Keutmann, H, and Cobb, S The

and exophthalmic goiter. In the remaining 17 cases, 2 of the patients showed signs of involvement of the central nervous system,⁶ probably in the nature of amyotrophic lateral sclerosis, the other 15 cases⁷ were largely instances of external ophthalmoplegia occurring during the course of thyrotoxicosis with exophthalmos. Presumably the majority of isolated palsies of the extraocular muscles occurring in association with exophthalmic goiter are due to the mechanical distortion of the structures of the orbit or to other causes unrelated to myasthenia gravis. The presence of palsy of the extraocular muscles is not in itself pathognomonic of myasthenia gravis. Neither can the presence of lymphorrhages in the muscles be considered conclusive evidence of the presence of myasthenia gravis, for, as Dudgeon and Urquhart⁸ have shown, these lymphocytic collections are present in 8 of 9 cases of exophthalmic goiter. More recently it has been shown that lymphorrhages are present in other conditions, such as myositis. The occurrence, however, of palsy of the extraocular muscles even in exophthalmic goiter is far from common. Heuer^{7a} stated that in a series of 300 cases of exophthalmic goiter in only 1 case (which he reports) was there evidence of such paralysis. Since palsy of the extraocular muscles is not common in hyperthyroidism, one may

Electromyogram in Myasthenia Gravis, *Brain* **51** 508, 1928. (g) Cohen, S. J., and King, F. H. Relation Between Myasthenia Gravis and Exophthalmic Goiter, *Arch Neurol & Psychiat* **28** 1338 (Dec.) 1932.

6 Burger, W. Ueber Thyrotoxikose mit spinalen Symptomen, *Deutsches Arch f. klin. Med.* **162** 355, 1928. Sterling, W. Maladie de Basedow, myasthémie, et amyotrophie progressive, *Rev. neurol.* **1** 93 (Jan.) 1930.

7 (a) Heuer, G. J. The Cerebral Nerve Disturbances in Exophthalmic Goiter, *Am. J. M. Sc.* **151** 339, 1916. (b) Bristowe, J. S. Cases of Ophthalmoplegia Complicated with Various Other Infections of the Nervous System, *Brain* **8** 313, 1885. Féreol, M. Report of a Case, *Gaz. hebdomadaire de médecine* **26** 112, 1889. Finlayson, J. On the Paralysis of the Third Nerve as a Complication of Grave's Disease, *Brain* **13** 383, 1890. Maude, A. A Case of Ophthalmoplegia with Grave's Disease, *ibid.* **15** 121, 1892. Posey, W. C. Palsy of the Extraocular Muscles in Exophthalmic Goiter, *Am. J. M. Sc.* **128** 66, 1904. Kappis, M. Ueber Gehirnnervenlahmungen bei der Basedowschen Krankheit, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **22** 657, 1910. Bernhardt, M. Basedowsche Krankheit und Augenmuskellähmung, *Neurol. Centralbl.* **30** 706, 1911. McKendree, C. A. A Case of Myasthenia Gravis, *J. A. M. A.* **63** 1553 (Oct. 31) 1914. den Boer, M. Goiter with Total Ophthalmoplegia, *Nederl. tijdschr. v. geneesk.* **1** 2284, 1920. Jackson, A. S., and Bates, A. D. Myasthenia Gravis, *J. A. M. A.* **81** 114 (July 14) 1923. Jaensch, P. A. Augenmuskellähmungen bei Basedowscher Krankheit, *Deutsche med. Wchnschr.* **50**:1249, 1924. Wedd, M. A., and Permar, H. H. Ophthalmoplegia in Grave's Disease, *Am. J. M. Sc.* **175** 733, 1928. Garvey, J. L. Ophthalmoplegia and Grave's Disease, *Ann. Int. Med.* **3** 917, 1930. Schonberg, H. Grenzfall von Morbus Basedowii und Myasthenia gravis pseudoparalytica, *Deutsche med. Wchnschr.* **63** 738, 1937.

8 Dudgeon, L. S., and Urquhart, H. L. Lymphorrhages in Exophthalmic Goiter, *Brain* **49** 182, 1926.

safely assume that the coexistence of myasthenia gravis and exophthalmic goiter is very rare, as the vast majority of patients with myasthenia gravis have such paralysis. As Naffziger⁹ pointed out, the palsies of the extra-ocular muscles encountered with hyperthyroidism are chiefly associated with exophthalmos, which was never present in the case here presented.

In the case reported here it was evident that when the manifestations of hyperthyroidism were at their height the symptoms of myasthenia gravis were at a minimum, and as the thyrotoxicosis waned the myasthenia reappeared. In the case reported by Wolff, Keutmann and Cobb^{5f} the myasthenia did not appear until after thyroidectomy, and then the patient's periods of the greatest strength coincided roughly with the periods in which the basal metabolic rate was highest. The patient in the case reported by Cohen and King^{5g} showed evidence of exophthalmic goiter and received roentgen therapy over the thyroid gland. It was only after this irradiation and the consequent reduction in the basal metabolic rate that the symptoms of myasthenia appeared.

The fact that abnormalities of the thymus gland occur in 50 per cent of cases both of myasthenia gravis¹⁰ and of exophthalmic goiter¹¹ has been used to link the two conditions. But whereas in exophthalmic goiter the abnormality consists of persistence or simple hyperplasia of the thymus gland, in myasthenia gravis thymic neoplasms of various types are usually found.

All these factors, the extreme rarity of cases in which the two diseases coexist, the fact that in these rare cases a "seesaw" type of balance seems to occur and the fact that the administration of a sufficient amount of potent thyroid extract to a myasthenic patient effected a reduction of myasthenic symptoms, appear to support a hypothesis that the two diseases are mutually antagonistic. The thymic abnormalities and the lymphorrhages which occur in both diseases are not sufficiently pathognomonic of either condition to be proof of any similarity in the two.

SUMMARY AND CONCLUSIONS

A case of myasthenia gravis is presented in which the appearance of hyperthyroid symptoms was attended by a lessening of the myasthenic symptoms. The administration of thyroid substance to a patient with

9 Naffziger, H. C. Progressive Exophthalmos Associated with Disorders of the Thyroid Gland, *Ann Surg* **108** 529, 1938. Lymphorrhages in Ocular Muscles. "One of the patients suffered from myasthenia in addition to exophthalmic goiter."

10 Norris, E. H. Thymoma from Unusual Case of Myasthenia Gravis, with Observations on General Pathology, *Am J Cancer* **30** 308, 1937.

11 Means, J. H. The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 289.

uncomplicated myasthenia gravis coincided with a period of remission of the myasthenic symptoms. In two cases previously reported by others^{5f,g} there was some evidence of this same type of "seesaw" balance between myasthenia gravis and exophthalmic goiter. For these reasons it is suggested that the two diseases are mutually antagonistic. Lastly, it is felt that this relation is a matter of scientific, but not of immediate therapeutic, importance.

HEART FAILURE IN SUBACUTE BACTERIAL ENDOCARDITIS

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AND

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Heart failure is often regarded as one of the important negative features of subacute bacterial endocarditis. Attention has been repeatedly directed to the absence of myocardial insufficiency in the disease. In this respect subacute bacterial endocarditis has been contrasted with rheumatic carditis, in which heart failure may be prominent in the clinical picture and may exist in a chronic and advanced form. However, it is generally admitted that heart failure may make its appearance during the late stages of the disease. Toxemia, a prominent factor in subacute bacterial endocarditis, has commonly been considered causal.

A short outline of the literature concerning the role of heart failure in subacute bacterial endocarditis is given in this paper, and the opinions on the character and extent of the anatomic changes in the myocardium in this disease are discussed. Observations in 40 cases of subacute endocarditis are presented, with special attention to evidence of heart failure and anatomic changes in the heart. A short discussion of these findings concludes the study.

REVIEW OF LITERATURE

Horder¹ wrote that arrhythmia, symptoms of inadequate response to effort, signs of dilatation of the heart and the results of so-called decompensation not only may be conspicuous by their absence but are unusual. He also stated that there is some difference in the views of different observers as to the relative incidence of the classic signs and symptoms of heart failure toward the end of the course of the disease. He stressed that there is general agreement that for the major part of its course subacute bacterial endocarditis is largely destitute of cardiac features.

From the Departments of Internal Medicine and Pathology, the Michael Reese Hospital.

Presented at the eleventh annual meeting of the Central Society for Clinical Research, Chicago, Nov 4, 1938.

1 Horder, T. Discussion on the Clinical Significance and the Course of Subacute Bacterial Endocarditis, *Brit M J* 2 301, 1920.

Libman² stated that it is a remarkable fact that in many cases of the usual type there are no evidences of cardiac insufficiency until late in the course of the disease. In that less frequently encountered condition designated as the "bacteria-free stage" of subacute bacterial endocarditis, he noted³ that myocardial insufficiency is a much more marked feature than it is in the active bacterial stage.

Thayer⁴ expressed the opinion that the terminal features of infective endocarditis are generally those of grave septicemia. He observed striking myocardial insufficiency in only one fourth of 99 cases in which he followed the disease to a fatal termination.

Lewis⁵ remarked that cardiac failure with congestion is rarely present in the early stages of this disease but is so frequent in the later stages as to be one of the chief causes of death.

A number of other clinical observers have expressed agreement with the foregoing opinions.⁶

Only a few investigators have made a study of the myocardial lesions associated with subacute bacterial endocarditis. The contributions of the following authors represent existing opinions.

Lewis⁵ stated that there are no recognizable lesions in the heart muscle.

Libman⁷ remarked that the essential lesion in the myocardium is an interstitial round cell infiltration, the so-called Bracht-Wachter bodies, that the lesions are not present in all cases and that they are not specific.

Starling⁸ stated that the myocardium does not suffer severely, despite the frequent observation of scattered foci of myomalacia with cellular infiltrations.

2 Libman, E. The Clinical Features of Subacute Streptococcus (and Influenzal) Endocarditis in the Bacterial Stage, *M Clin North America* **2** 117, 1918.

3 Libman, E. A Consideration of the Prognosis in Subacute Bacterial Endocarditis, *Am Heart J* **1** 25, 1925.

4 Thayer, W. S. Observations on Rheumatic Pancarditis and Infective Endocarditis, *Ann Int Med* **5** 247, 1931.

5 Lewis, T. Diseases of the Heart, ed 2, New York, The Macmillan Company, 1937.

6 (a) White, P. D. Heart Disease, ed 2, New York, The Macmillan Company, 1937. (b) Blumer, G. Subacute Bacterial Endocarditis, *Medicine* **2** 105, 1923. (c) Fishberg, A. M. Heart Failure, Philadelphia, Lea & Febiger, 1937. (d) Laws, C. L., and Levine, S. A. Clinical Notes on Rheumatic Heart Disease with Special Reference to the Cause of Death, *Am J M Sc* **186** 833, 1933. (e) Cotton, T. F. Subacute Infective Endocarditis, *Brit M J* **2** 851, 1920.

7 Libman, E. Characterization of the Various Forms of Endocarditis, *J A M A* **80** 813 (March 24) 1923.

8 Starling, H. J. Endocarditis Lenta, *Quart J Med* **16** 263, 1922.

Without reference to the type and character of the anatomic change, Longcope⁹ mentioned that some form of lesion may be observed in one-half the cases in which autopsy is performed

Blumer^{6b} stated that chronic interstitial myocarditis was noted in 8 of 150 hearts, acute myocarditis in 2, small abscesses in 3 and focal necrosis and infarcts each in 2

The contributions of Clawson,¹⁰ which appeared a decade ago, are noteworthy in emphasizing the extensive inflammatory change occurring in the heart muscle in subacute bacterial endocarditis. Clawson stated that myocarditis is more frequent in subacute bacterial endocarditis than in acute and recurrent rheumatic endocarditis and that the greater frequency of abscesses in subacute bacterial endocarditis than in other forms of endocarditis is accounted for by the lodging in the myocardium of infected emboli from the valves

One of us (Saphir¹¹) described fairly widespread inflammatory and degenerative changes consisting chiefly of focal necrosis, minute infarcts, Aschoff bodies and perivascular fibrosis. The most frequent and characteristic lesions were minute infarcts

In summary, the following two points are brought out. 1. Heart failure frequently accompanies subacute bacterial endocarditis but is present during only a small fraction, usually the terminal part, of its course. The emphasis is clearly on the lack of any appreciable part played by it in the general course of the disease. 2. In descriptions of the character and extent of the myocardial lesions in this disease one notes a great diversity of opinion. In fact, observations indicate a gamut of changes ranging from none at all to changes of considerable severity and magnitude, the general opinion being that the structural alterations are without much significance

It seems a remarkable fact, too, that the literature discloses few studies of the extracardiac lesions which would denote the existence of previous heart failure of some intensity and chronicity. We refer to the presence of chronic passive hyperemia of the lungs, liver and other viscera. Such evidence, when of sufficient grade, connotes heart failure and affords information highly pertinent to the question. Blumer found such evidence and reported chronic passive hyperemia of the lungs in 30 cases and of the liver in 53

9 Longcope, W. T. The Differentiation of Acute Rheumatic Fever from Bacterial Endocarditis, *M. Clin. North America* **16** 1029, 1933

10 Clawson, B. J. Myocarditis, *Am. Heart J.* **4** 1, 1928

11 Saphir, O. Myocardial Lesions in Subacute Bacterial Endocarditis, *Am. J. Path.* **11** 143, 1935

MATERIAL AND METHODS

Ten of the 40 patients with subacute bacterial endocarditis came under our clinical observation. The clinical data on 30 cases were furnished solely by the hospital records. It becomes a matter of great importance to find in these records clearcut descriptions of the objective findings indicating beyond question the presence of heart failure. Since the expression heart failure is used to designate clinical states varying between those showing only signs of exhaustion of the cardiac reserve and those exhibiting advanced congestive failure, it was thought advisable to consider only cases in which objective signs were present as those of heart failure. Edema of the dependent parts, fluid in the serous sacs, rales over the bases of the lungs and hepatic enlargement were relied on as signs necessary for the diagnosis of heart failure. It is, of course, difficult to affix a definite time to the advent of heart failure in a patient by studying the record alone. To admit less error and to conform to the scope of this paper, we made the diagnosis only when the objective symptoms were of a magnitude indicating beyond doubt the presence of the condition. The possibility of edema of renal origin has been excluded as carefully as possible.

It becomes necessary to define the disease process itself. What is subacute bacterial endocarditis? We are aware of the fact that anatomically subacute bacterial endocarditis may be difficult to differentiate from acute bacterial endocarditis. From our experience, based on combined clinical and anatomic observations, we have set forth certain diagnostic criteria, the presence of a majority of which is taken to favor the diagnosis of subacute bacterial endocarditis. These criteria are as follows: (1) large vegetations, (2) evidence of old valvular lesions (rheumatic, nonspecific, syphilitic or congenital malformations), (3) involvement of the adjacent mural, auricular and ventricular endocardium and the chordae tendineae, (4) minute ulcerations of the cusps or leaflets of the valve, and (5) the presence of cocci in chains in sections of the vegetations.

An autopsy was performed in every instance, and special attention was given to the valvular changes in the heart and to the gross and histologic appearance of the myocardium, lungs, liver, spleen and kidneys. Blocks were taken from these organs, fixed in solution of formaldehyde and embedded in paraffin. Most commonly the hematoxylin-eosin stain was used, though special stains were employed when necessary. A more detailed histologic study of the myocardium of some of these hearts has been reported previously.¹¹

The principal organs examined for chronic passive hyperemia were the lungs, liver, spleen and kidneys. The degree of chronic passive hyperemia in these organs was judged arbitrarily, the changes being classified as 1 plus, 2 plus, etc. In the lungs, for instance, the amount of connective tissue proliferation, the relative number of heart failure cells and the presence of red blood cells determined the stage of chronic passive hyperemia. In the liver the extent of dilatation of the sinusoids, the accompanying changes in the liver cells and the amount of connective tissue in the periportal spaces were used in the determination of the degree of chronic passive hyperemia. It should be stressed in this connection that whenever there was the slightest doubt as to the classification of the degree of passive hyperemia of the various organs, the condition was placed in the lower of the two categories in question.

RESULTS

Eighteen, or 45 per cent, of our 40 patients showed frank clinical signs of heart failure, such as distention of the veins of the neck, edema

of the dependent parts, enlargement of the liver, fluid in the serous sacs and rales at the bases of the lungs. In all of these 18 patients autopsy revealed chronic passive hyperemia of the viscera, and most of them had appreciable collections of fluid in the serous sacs. Heart failure of an advanced grade was exhibited clinically by 11 of these 18 patients. In the other 22 patients there were no clinical signs of myocardial insufficiency. In 12 of the 22 patients autopsy showed a grade of chronic passive hyperemia of the lungs, liver and other viscera hardly less than that seen in the former group of 18 patients. A few of the aforementioned 12 patients had accumulations of fluid in the serous sacs that escaped clinical recognition. This is taken as evidence that heart failure of some grade must have been present for some time before death. For the groups studied clinically and that studied pathologically the frequency of heart failure was 75 per cent. The remaining 9 patients had no chronic passive hyperemia and no clinical evidence of heart failure.

Eight patients seen for the first time were observed to have heart failure at the time of their admission to the hospital, in 10 the development of heart failure was noted during the course of the disease. In all instances in which heart failure was observed it was continuous and progressive and extended from two weeks to two months. Five of the 8 patients admitted to the hospital with heart failure died approximately one week after admission, the remaining 3 had heart failure for a period roughly between one and two and one-half months. The average duration of the disease in 18 patients with heart failure was eight months, in the remaining patients it was approximately five months. The clinical course of 6 of the 10 patients in whom no chronic passive hyperemia of the organs was present was abruptly terminated by embolic accidents.

All the hearts with gross lesions typical of subacute bacterial endocarditis invariably showed large vegetations and evidence of older endocardial lesions. Also, the mural endocardium was always involved. Except in 2 hearts, the underlying lesions of the endocardium were those of either true rheumatic endocarditis or of endocarditis the cause of which could not be determined but which resembled morphologically the rheumatic type. In 1 of the 2 exceptions the heart was the seat of a congenital anomaly (patency of the intraventricular septum, and toramen primum). Most of the vegetations were seen in the vicinity of the defects. In the second instance there was syphilitic aortitis with involvement of the aortic valve.

Generally the myocardium grossly was light grayish brown, and often yellow dots and streaks were seen, suggesting fatty degeneration of the myocardium. In some instances on section the myocardium seemed bulging. Its normal architecture was obscured. Grayish dots and streaks were especially clear in the wall of the left ventricle.

Most of the gross evidence of chronic passive hyperemia at autopsy was in the liver and the lungs. The passive hyperemia in the spleen and in the kidneys was sometimes obscured by acute hyperplasia of the spleen and acute nephritis, respectively. The degree of chronic passive hyperemia in the various organs is given in table 1.

Histologic examination of the myocardium revealed significant changes. In 14 instances abscesses were seen in the myocardium, most commonly that of the left ventricle was involved, and occasionally the intraventricular septum close to the endocardium of the left ventricle. Often areas of necrosis were seen, with only a few polymorphonuclear leukocytes. These foci of necrosis were interpreted as early abscesses. Occasionally polymorphonuclear leukocytes were seen in the interstitial

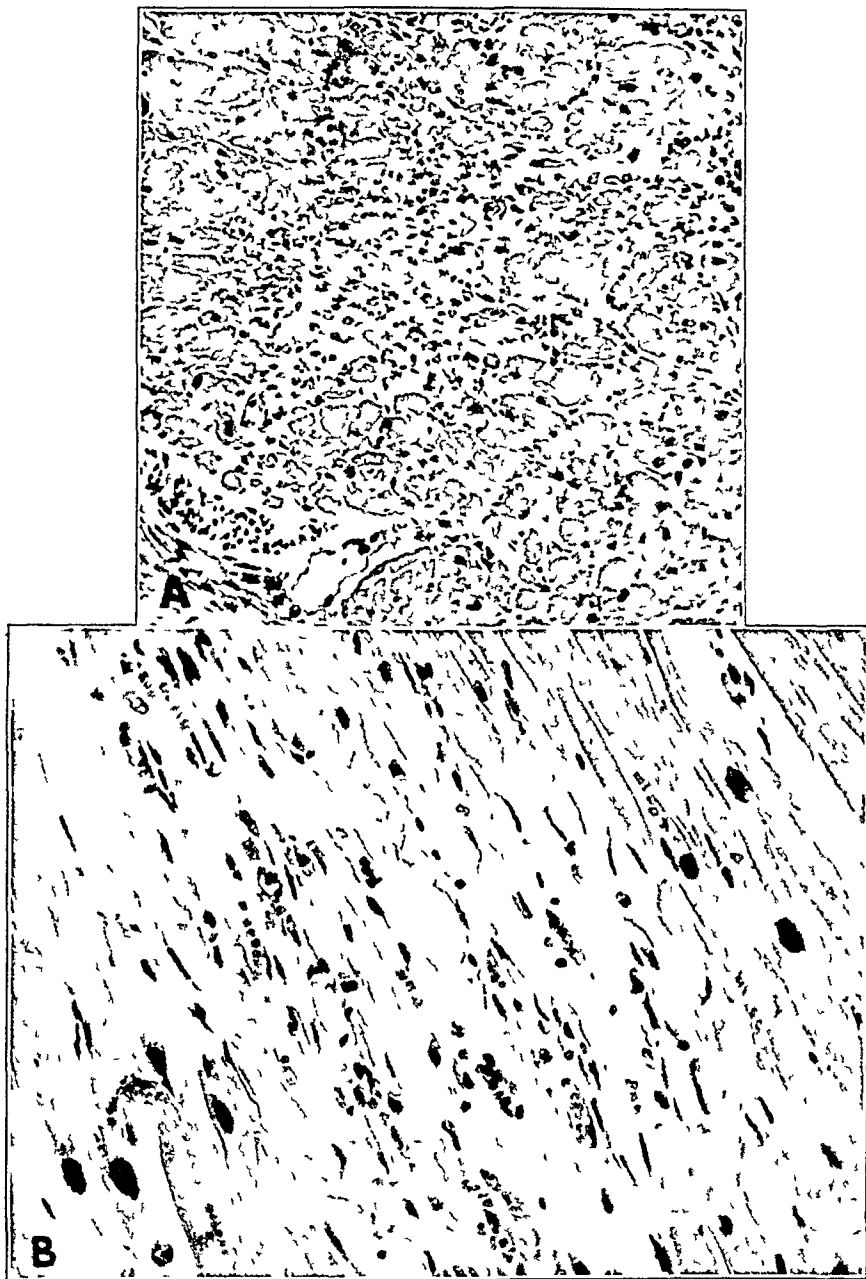
TABLE 1—*Degree of Chronic Passive Hyperemia*

Case No	Lungs	Liver	Spleen	Kidneys	Case No	Lungs	Liver	Spleen	Kidneys
1	+	+	—	—	21	++	++	—	—
2	++	++	++	+	22	++++	++++	++	+
3	++	++	+	+	23	—	—	—	—
4	++	++	++	+	24	+++	++	++	—
5	++++	++++	++++	+++	25	+	+	—	—
6	+++	+++	+++	++	26	—	+	+	—
7	—	—	—	—	27	++	+	+	—
8	+++	+++	+++	++	28	+	++	+	—
9	—	+	+	—	29	—	+	+	—
10	—	—	—	—	30	++	++	+	—
11	+++	++	+	—	31	++++	++++	+++	+
12	++	++++	+++	++	32	+++	++	+++	—
13	+++	+++	+++	+	33	+++	+++	++	+
14	++	++	+	—	34	—	—	—	—
15	++	++	++	—	35	—	—	—	—
16	++	+++	++	+	36	++	+++	+++	+
17	++	++	++	+	37	++	++	++	—
18	+++	++++	++++	++	38	+++	+++	+++	+
19	++++	++++	+++	—	39	++++	++++	++++	++
20	++++	++++	+++	+	40	+++	++	++	+

tissue, close to the blood vessels, but areas of necrosis were negligible in these regions. Perivascular areas of subacute and chronic inflammation were also encountered. Often the inflammatory cells were mainly lymphocytes, and occasionally a few polymorphonuclear leukocytes were intermingled with the lymphocytes. Perivascular fibrosis was rather common. It was observed in those hearts which showed Aschoff bodies but also was occasionally present in the absence of Aschoff bodies. In 15 instances Aschoff bodies were observed in the myocardium. Only cellular accumulations which unquestionably were typical Aschoff bodies, as described in a previous study,¹² were so designated. They were typically located in a perivascular situation and were observed to be independent of other changes in the same heart. The most consistent changes in the myocardium were the replacement of heart muscle fibers

12 Saphir, O, and Wile, S. A. Rheumatic Manifestations of Subacute Bacterial Endocarditis in Children, *Am Heart J* 9 29, 1933

by many spindle-shaped cells with a few lymphocytes and a number of phagocytic cells, the cytoplasm containing granules of brown pigment. Often a scant new formation of connective tissue fibers and small



A ($\times 150$), minute infarct in the myocardium, *B* ($\times 250$), organizing infarct in the myocardium. Hematoxylin-eosin preparation.

Lesions like these are most frequently encountered in the myocardium of patients with subacute bacterial endocarditis.

blood vessels was also present in these regions. These areas could easily be interpreted as organizing infarcts. A diligent search sometimes revealed emboli in the smaller branches of the coronary arteries in

the vicinity of these regions. The emboli consisted most commonly of amorphous débris which morphologically resembled the superficial portions of vegetations. These infarcts were present in 27 instances. Table 2 shows the incidence of abscesses, Aschoff bodies, minute infarcts, emboli, perivascular fibrosis and inflammatory changes in the myocardium. It also gives the degree of chronic passive hyperemia

TABLE 2—*Myocardial Changes in Subacute Bacterial Endocarditis*

Case No	Age, Yr	Clinical Evidence of Heart Failure	Foci of Necrosis and Abscesses	Minute Infarcts	Emboli	Aschoff Bodies	Perivascular Fibrosis	Acute and Chronic Inflammation	Chronic Passive Hyperemia in Various Organs*
1	5		+			+		Acute	0
2	19			+		+	+		+
3	50		+	+	+				+
4	29	+	+						+
5	53	+		+		+	+		++++
6	19	+	+	+	+			Chronic	+++
7	19		+	+	+	+			0
8	41	+		+	+	+	+		+++
9	10			+		+	+	Chronic	0
10	13		+	+	+	+	+		0
11	11			+		+	+	Chronic	++
12	29	+		+			+		++
13	29	+		+			+	Chronic	+++
14	35	+	+		+				+
15	32	+	+	+	+		+		++
16	43	+		+	+		+	Chronic	++
17	46						+	Chronic	++
18	42	+		+	+		+		++++
19	21		+					Acute	+++
20	62	+		+					+++
21	13					+	+		+
22	6		—	—	+	+	+		++
23	23			+	+			Chronic	0
24	73	+			+	+	+	Chronic	++
25	48			+					0
26	41			+	+		+		0
27	25	+	+		+	+	+	Acute	+
28	47		—				+		+
29	42		+	+			+		0
30	51		+				+	Chronic	+
31	29			+	+	+			+++
32	30			+			+	Acute	++
33	32	+		+				Acute	++
34	38			+	+			Acute	0
35	38			+	+	+	+		0
36	15			+	+			Acute	++
37	50	+					+	Acute	++
38	19	+		+	+			Acute	+++
39	29	+		+	+				++++
40	42	+						Chronic	++

* In determining the degree of chronic passive hyperemia the amount of free fluids in the various cavities was also taken into consideration.

which was observed in the various organs and states whether or not there was clinical evidence of heart failure.

An analysis of this table indicates that there is no relation between the presence of Aschoff bodies, abscesses or infarcts and chronic passive hyperemia as demonstrated at autopsy. In some instances in which Aschoff bodies were observed in the myocardium there was only slight chronic passive hyperemia in the various organs, while in other instances in which the myocardium showed a variety of anatomic lesions exclusive

of Aschoff bodies chronic passive hyperemia was severe. Extensive infarction of the heart following coronary embolism occurred in 1 case. The patient exhibited advanced congestive heart failure of two months' duration.

It may be of interest to emphasize that Aschoff bodies were observed in 15 hearts, an incidence of 37 per cent, 9 of the patients were under 20 and 6 were over 25 years of age. In only 3 of these 15 patients was heart failure observed clinically. At autopsy chronic passive hyperemia was observed in 10 of the 15 cases, an incidence practically the same as that for the entire series of 40 cases.

COMMENT

From an examination of our data two pertinent facts are brought out: first, that heart failure occurs more frequently in subacute bacterial endocarditis than is commonly believed, and, second, that the heart muscle is the seat of widespread anatomic change.

It will be readily appreciated that because of lack of unanimity of opinion concerning the anatomic relation, confusion must exist in the explanations of the cause of heart failure, which we have noted to occur so frequently in this disease. Those who maintain that the heart shows no or minimal change must necessarily advance some explanation for the failure on the basis of function, and these explanations have not been wanting. Frequently one encounters statements to the effect that "poisoning," "exhaustion," "strain" or a combination of these is causal. On the other hand, those who realize, as we do, that there are ample structural alterations to explain the occurrence of heart failure may readily place it on an anatomic basis.

While it is true that arterial embolism, sepsis, toxemia and cachexia are the cardinal symptoms of the disease, heart failure of some grade and chronicity has to be reckoned with as a feature of the disease. Our material is too meager to controvert the rather common opinion that it is a terminal event. The average duration of the disease in our series was only a little over six months. In point of absolute duration, the heart failure occurring in subacute bacterial endocarditis must necessarily be relatively short, although our data indicate chronicity of some degree. This ratio may compare favorably with that for other inflammatory and degenerative diseases of the heart requiring a decade or two for their resolution. It would be intriguing, if it were possible, to discern major differences in the clinical pattern in the different forms of heart disease. There has been so much emphasis on the absence of heart failure in subacute bacterial endocarditis until the very late stages that a "pattern" here appears well defined. After critical examination of what has been said on this matter and analysis of our own data it is difficult to discern real differences between the disease under discussion

and other forms of heart disease. In the presentation of a series of cases so limited as this the question arises as to whether they are "representative," for the disease is one of great variability and is often shortened by embolic accidents. On this point it may be said that many reports dealing with the subject are based on series no larger than ours.

The lack of significant alterations in the electrocardiograms of patients with subacute bacterial endocarditis has further supported the popular contention that the heart muscle escapes any significant structural change in this disease. In the electrocardiographic studies of Rothschild, Sacks and Libman¹³ and also in those of Levy and Turner,¹⁴ this feature has been contrasted with the observations in cases of rheumatic infection, in which abnormalities in the ST segment and other electrocardiographic changes are frequently noted in serial curves. In commenting on this point, Swift¹⁵ accepted this as evidence of the "lack of parenchymatous irritation" in the heart in subacute bacterial endocarditis. From the conclusions reached by Rothschild, Sacks and Libman¹³ one can only infer that serial curves were obtained on patients with subacute bacterial endocarditis, though the authors have clearly indicated that they were obtained on patients in the rheumatic group. Levy and Turner¹⁴ were careful to state that graphic records for the nonrheumatic group were secured at less frequent intervals. They studied the records of only 23 patients with subacute bacterial endocarditis and compared them with those of 403 patients comprising the rheumatic group. With the disproportionately large number of patients in the latter who were followed more systematically, it is obvious that no conclusions as to the comparative frequency of electrocardiographic alterations in the two groups may be justly drawn. With lesions so widespread as we found them in the myocardium a high incidence of electrocardiographic alterations might be expected to be found in serial curves. Unfortunately, our material is too fragmentary to make possible any comment except that significant changes in the ST segment and the T wave were observed in the few cases so studied. If the Aschoff bodies are responsible for the fleeting changes seen in the electrocardiogram in acute rheumatic infection (Cohn and Swift¹⁶ admitted this possibility), it may be pertinent to ask why Aschoff bodies in the myocardium in cases of subacute bacterial endocarditis should not cause

13 Rothschild, M. A., Sacks, B., and Libman, E. The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *Am Heart J* **2** 356, 1926.

14 Levy, R. L., and Turner, K. B. Impaired Auriculoventricular Conduction in Rheumatic Fever. A Comparative Study with Diagnostic Applications, *Arch Int Med* **43** 267 (Feb) 1929.

15 Swift, H. F. The Heart in Infection, *Am Heart J* **3** 629, 1928.

16 Cohn, A. E., and Swift, H. F. Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J Exper Med* **39** 1, 1924.

similar electrocardiographic changes. This question is raised merely for argument, for apart from the presence of Aschoff bodies, which are frequently seen in association with subacute bacterial endocarditis (they were present in 37.5 per cent of our cases), there are other lesions which might readily produce all the fleeting electrocardiographic changes seen in cases of rheumatic disease. It also may be worth while to comment that when this study was first undertaken it was thought that the coexistence of specific rheumatic infection and subacute bacterial endocarditis would serve as a clue to the development of heart failure in the latter disease, a presumption which was not borne out.

The study of the myocardium clearly indicates why heart failure was present in some instances. As a matter of fact, in the light of these investigations it seems remarkable that chronic passive hyperemia was not more pronounced than it was, because of the severe changes in the myocardium in almost every instance. It is remarkable that the myocardium may be as severely damaged as in some of our cases and chronic passive hyperemia be relatively slight. From this study it also seems clear that there is no distinct relation between anatomic myocardial changes and clinical evidence of heart failure. From the anatomic point of view, moreover, it is difficult to believe that a patient whose myocardium is so severely damaged does not show more clinical evidence of myocardial failure. On the other hand, when heart failure was present in these cases of subacute bacterial endocarditis, anatomic changes in the myocardium were invariably observed. It seems evident that in some patients with severe myocardial changes the reserve power of the undamaged myocardial fibers is so great that there is little evidence of heart failure and, vice versa, that in other patients with fewer anatomically demonstrable myocardial changes the reserve power of the apparently unharmed muscle is so limited that heart failure ensues. Of course, the presence of toxemia with dilatation of the capillary bed should also be considered in explanation of the heart failure, but it seems probable that such hypothetical paralysis of the vascular bed is present in all cases of subacute bacterial endocarditis, with severe or with less severe myocardial lesions. Yet some of the patients die with no or with slight clinical evidence of heart failure, while others exhibit evidence of severe heart failure. It seems, therefore, that there is no relation between heart failure and demonstrable damage of the myocardium. It appears, rather, that the state of the apparently undamaged muscle determines whether the myocardium in these instances becomes insufficient or whether it is able to maintain its function. To this intangible and varying reserve power of the uninvolved muscle fibers, which also governs the fate of the infarcted arteriosclerotic heart, must be ascribed the apparent discrepancy between clinically observed heart failure in one patient and its absence in another.

SUMMARY AND CONCLUSIONS

Heart failure of a fairly advanced grade was seen in 18 of 40 patients with subacute bacterial endocarditis, a clinical frequency of 45 per cent. At necropsy the various organs showed a marked degree of chronic passive hyperemia in every instance, and there were frequently accumulations of fluid in the serous sacs.

The presence of marked chronic passive hyperemia of the lungs, liver and other viscera in 12 additional patients in whom the heart failure was not recognized clinically indicates that here, too, it must have been present for some time. The combined frequency of heart failure for the groups studied pathologically and that studied clinically was 75 per cent.

Ten patients had no chronic passive hyperemia. The clinical course of 6 of these was terminated by the rupture of mycotic aneurysms.

Extensive myocardial lesions are observed uniformly in patients who die of subacute bacterial endocarditis. They consist of minute emboli, infarcts and abscesses, diffuse inflammation, Aschoff bodies and perivascular fibrosis.

These structural alterations are adequate to explain the advent of heart failure in this disease. They are of such magnitude and intensity as to make it remarkable that heart failure is not even more marked than we found it to be.

It is not necessary to invoke such general causes as toxemia or exhaustion to explain the advent of heart failure in subacute bacterial endocarditis.

The coexistence of rheumatic myocarditis and subacute bacterial endocarditis cannot be considered causal in the development of heart failure.

CLINICAL SIGNIFICANCE OF VARIATIONS IN SERUM PHOSPHATASE IN HEPATIC AND BILIARY DISORDERS

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During the eight years that followed Roberts'¹ observation of an increase in serum phosphatase in the presence of jaundice, numerous statistical studies and many experiments have been carried on to evaluate it as an aid in differential diagnosis. The mechanism accounting for the rise in serum phosphatase has not been satisfactorily described. Roberts stated that there is a pronounced increase in phosphatase in obstructive and in catarrhal jaundice. He suggested that this denotes nothing more than an expression of the presence of bile constituents in the blood, since bile itself has a high phosphatase content. In 1933 he² stated that this premise does not explain all the facts. He reached the conclusion, based on a study of 52 cases, that toxic, infective and catarrhal jaundice may be readily distinguished from jaundice of the obstructive type by characteristic values of phosphatase.

Subsequent investigators have not found this to be the case in the two types of jaundice. A review of the literature can be found in the articles by Greene, Shattuck and Kaplowitz,³ Rothman, Meranze and Meranze,⁴ Cantarow and Nelson⁵ and Flood, Gutman and Gutman⁶. Some of the

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Dr Max Lederer, Director

1 Roberts, W M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit J Exper Path* **11** 90, 1930

2 Roberts, W M. Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit M J* **1** 734, 1933

3 Greene, C H, Shattuck, H F, and Kaplowitz, L. Phosphatase Content of Blood Serum in Jaundice, *J Clin Investigation* **13** 1079, 1934

4 Rothman, M M, Meranze, D R, and Meranze, T. Blood Phosphatase as an Aid in the Differential Diagnosis of Jaundice, *Am J M Sc* **192** 526, 1936

5 Cantarow, A, and Nelson, J. Serum Phosphatase in Jaundice, *Arch Int Med* **59** 1045 (June) 1937

6 Flood, C A, Gutman, E B, and Gutman, A B. Phosphatase Activity, Inorganic Phosphorus and Calcium of Serum in Disease of the Liver and Biliary Tract. Study of One Hundred and Twenty-Three Cases, *Arch Int Med* **59** 981 (June) 1937

investigators have substantiated the findings of Roberts, namely, that the serum phosphatase value is greater than 10 units in cases of obstructive jaundice while in the hepatocellular form of jaundice, which includes the toxic and the infective type, the value is 10 units or less. Rothman and his co-workers found this test to be of greater clinical value than any other available test in differentiating between obstructive and non-obstructive jaundice. Other investigators, however, found such variable results in cases of hepatocellular jaundice that they concluded the test to be unreliable. For example, Cantarow and Nelson found that the serum phosphatase was below 10 units in 24 per cent of 50 cases of obstructive jaundice and in 36.6 per cent of 41 cases of hepatocellular jaundice, an observation which limits the practical significance of serum phosphatase from the standpoint of differential diagnosis.

The results of experimental procedures also have not been constant. By ligating the common bile duct in dogs, Bodansky and Jaffe,⁷ Armstrong, King and Harris⁸ and Thannhauser and his co-workers⁹ produced a marked and progressive rise in serum phosphatase. A similar procedure in cats did not cause a rise. Hartman and Schelling,¹⁰ Armstrong and King¹¹ and Freeman, Chen and Ivy¹² produced hepatic damage by different methods and noticed an increase in the serum phosphatase.

Flood and his colleagues⁶ suggested that some of these inconsistencies may be due to the method used in estimating phosphatase activity. They pointed out that there are important differences in the classifications of jaundice employed by various investigators, as well as in the criteria considered necessary for definitely establishing the cause and type of jaundice. They finally pointed out the difficulty of drawing a sharp distinction between obstructive and hepatocellular jaundice for diagnostic purposes, it is probable that in the latter disorder also obstruction plays some role.

7 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. Increase of Serum Phosphatase After Bile Duct Ligation in the Dog, *Proc Soc Exper Biol & Med* **31** 1179, 1934.

8 Armstrong, A. R., King, E. J., and Harris, R. I. Phosphatase in Obstructive Jaundice, *Canad M A J* **31** 14, 1934.

9 Thannhauser, S. J., Reichel, M., Grattan, F. J., and Maddock, S. J. The Effect of Experimental Total Biliary Obstruction on the Serum Phosphatase Activation in Dogs and Cats, *J Biol Chem* **121** 697, 1937.

10 Hartman, F. W., and Schelling, V. Serum Phosphatase in Experimental Insufficiency of the Liver, *Arch Path* **18** 594 (Oct) 1934.

11 Armstrong, A. R., and King, E. J. Serum Phosphatase in Toxic and Hemolytic Jaundice, *Canad M A J* **32** 379, 1935.

12 Freeman, S., Chen, Y. P., and Ivy, A. C. On the Cause of the Elevation of Serum Phosphatase in Jaundice, *J Biol Chem* **124** 79 1938.

Cantarow and Nelson⁵ stated the belief that it is useless in the present state of knowledge to speculate about the possible mechanism which produces an increase of serum phosphatase in obstructive and hepatocellular jaundice. They pointed out that an increase cannot be explained, as implied by Heibert,¹³ on the basis of obstruction to the flow of bile, either extrahepatic or intrahepatic. Cases in which the icterus index is high in the presence of a normal value for serum phosphatase and in which serum phosphatase values are increased in the presence of a normal icterus index were reported by Greene and his colleagues³ and others. Rothman and his co-workers⁴ pointed out the importance of the relation of serum phosphatase to the icterus index as an aid in differential diagnosis. A value of about 10 units for serum phosphatase in the presence of an increasing icterus index points toward a hepatocellular disorder.

Thannhauser and his co-workers¹¹ threw much light on this subject by a series of experiments on dogs and cats and experiments *in vitro*. They interpreted the rise in serum phosphatase after biliary obstruction as due to increased activation of the enzyme and not to actual increase in the amount of circulating phosphatase as previously supposed. The bile of dogs contains from 25 to 55 units of phosphatase per hundred cubic centimeters, an indication of almost complete activation of the phosphatase in gallbladder bile. After producing a complete biliary fistula, the authors found a paradoxical increase in serum phosphatase. Further experiments demonstrated the ability of bile salts to decrease the activation of serum phosphatase. They concluded that what has always been regarded as an increase in the serum phosphatase in the presence of disease is not an actual increase in enzyme but merely an activation of phosphatase normally present. The mechanism of activation in jaundice is dependent on an activating substance (a cofactor, or coenzyme, which has not yet been isolated or identified) and a depressing substance (like bile salts). Therefore, when there is an obstruction damming up both, since the cofactor is more powerful as an activating agent than the bile acids as depressors, the net result is an increase in the activity of serum phosphatase. The authors stated that the resultant activation of phosphatase must represent the outcome of reactions in a complex system consisting of enzyme, oxidation-reduction potential and substrate. Human disease may therefore originate from an excess of any of the factors in the system. However, the experimental basis of these conclusions has recently been questioned, therefore, they must

13 Herbert, F. K. Plasma Phosphatase in the Various Types of Jaundice, *Brit J Exper Path* **16** 365, 1935

14 Thannhauser, S. J., Reichel, M., and Grattan, J. F. Studies in Serum Phosphatase Activity, *J Biol Chem* **121** 697, 1937

be held in abeyance for the present (King and Delory¹⁵ and Thannhauser, Reichel and Grattan¹⁶)

All investigators agree that serum phosphatase does not rise in cases of jaundice of purely hemolytic origin. It is on the application of this test as a means of differential diagnosis between hepatocellular and obstructive jaundice that the investigators disagree. In cases of obstructive jaundice the rise in serum phosphatase is fairly constant, and this fact has formed the basis of a valuable diagnostic test. This has been proved experimentally by ligating the common bile duct and noting the rise in serum phosphatase. In cases of hepatocellular jaundice, the results have been too variable to serve as a diagnostic aid, ranging from normal to increases of 50 units. The experimental procedures noted, produced to cause hepatic damage, have brought varying results, including marked increases. Thannhauser and Freeman, Chen and Ivy¹² even in the presence of a complete biliary fistula, noticed an increase in serum phosphatase. With the clinical observations and experimental results described, it has been a difficult and discouraging problem to account for the rise in serum phosphatase in order to use it as a clinical aid. The general confusion concerning this problem has been further increased by three types of clinical cases.

- 1 In some cases of cholecystitis, as reported by Cantarow and Nelson,⁵ Greene and his co-workers³ and confirmed in our studies, the icterus index is within normal limits or slightly elevated, but the value of serum phosphatase is increased even to 34 units. The cause for this increase has not been definitely explained hitherto.

- 2 In cases of congenital anomalies of the extrahepatic bile ducts in the newborn reported by Cantarow and Nelson⁵ and Thannhauser,¹⁷ in which the icterus index was markedly increased, the serum phosphatase values were, surprisingly, normal. This paradox, that obstruction exists and the serum phosphatase value is normal, has been difficult to explain.

It is interesting to note that here are two types of case in which the icterus index and serum phosphatase values do not show the usual relation. This has been noted before.

- 3 A third type of case exists, in which the biliary system is obstructed with resultant jaundice and the serum phosphatase value is normal or only slightly increased.

Correlation of the facts revealed by statistical data and experimental work has led to conclusions which have not always been consistent. For

15 King, E. J., and Delory, G. E. Ascorbic Acid and Phosphatase Activity, *Biochem J* **32** 1157, 1938.

16 Thannhauser, S. J., Reichel, M., and Grattan, J. F. The Effect of Ascorbic Acid on Beta-Glycerophosphate, *Biochem J* **32** 1163, 1938.

17 Thannhauser, S. J. Personal communication to the authors.

instance, it is known that the mucosa of the small intestine is relatively rich in phosphatase (Cantarow¹⁸). On the assumption that the enzyme passes into the portal stream through the same circuit as the bile pigments, even an hepatocellular obstruction should cause a constantly high serum phosphatase value if obstruction is the only factor involved. That this is not the case has already been shown. If all the phosphatase originates in the osseous system it is again difficult to explain its failure to rise in some cases of acute hepatitis when an obstruction is present as indicated by the accumulation of bile pigments in the blood stream. One might assume that the permeability of the cells of the liver through which the enzyme must pass is altered by certain constituents. The change in permeability may affect the enzyme or its activating substance in different ways, and this may account for the variable values in serum phosphatase.

The physiologic basis for the origin of this enzyme, its circulation and the influence of various substances on it, has been postulated by previous investigators. In addition to the physiologic factors, we¹⁹ investigated the underlying pathologic changes which cause increased phosphatase values in the serum. This was done by experimental work on dogs. In this publication the result of an attempt at clinical correlation between the disorders of the liver and the biliary system and the variable serum phosphatase values is described. Clinical and experimental evidence indicate that the liver cells play no part in the formation of bile pigment but merely secrete it into the bile ducts. In the case of phosphatase metabolism, however, the liver plays more than a passive role, and this probably explains the different values in the hepatocellular type of jaundice.

On the basis of our experiments we concluded that the most likely explanation is the production of phosphatase or an activating substance by the liver, when the liver cell is damaged the production of the activating principle or actual enzyme is diminished. Accordingly, the rise in serum phosphatase in cases of hepatic and biliary disorders probably is dependent on two factors: (1) the state of the liver cells and (2) the degree of biliary obstruction. We attempted to apply these conclusions to cases of hepatic and biliary disease, in all of which the underlying pathologic conditions of the hepatic parenchyma were borne in mind.

In cases of extrahepatic obstruction, the hepatic parenchyma differs microscopically from that in cases of hepatocellular jaundice in which it is damaged to varying degrees. The presence of some obstruction to

18 Cantarow, A. Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, *Internat Clin* **1** 230, 1936.

19 Schiffmann, A., and Winkelmann, L. Influence of the Liver on Serum Phosphatase, *Arch Int Med* **63** 919 (May) 1939.

the biliary system also in the latter condition has already been suggested by Flood and his colleagues⁶

A table of illustrative cases of various hepatic manifestations, in the majority of which some degree of hepatocellular jaundice occurred is presented. All the laboratory tests are listed in order to provide a basis for comparison and to indicate that their adequacy is limited unless the underlying pathologic state of the liver also is taken into account.

Certain cases in which diagnostic difficulties were encountered are reported briefly.

CASE 6—J A, a 24 year old white man, was admitted to the hospital complaining of an insidious onset of jaundice for the past year and enlargement of the abdomen. On admission his temperature, pulse, respiration and blood pressure were normal. The liver and spleen were enlarged. The impression was that the patient had hypertrophic biliary cirrhosis (Hanot's type).

CASE 7—L A, a 38 year old white woman, was admitted to the hospital complaining of epigastric pain, chills and icterus. Her liver was enlarged to the iliac crest and was tender. Five years before she had had a cholecystectomy. One year later stricture of the common bile duct developed, and she underwent an operation to transplant the uninvolved duct to the duodenum. The impression was that she was suffering from acute cholangitis. During her stay at the hospital pneumococcal sepsis and terminal acute endocarditis developed. Permission for autopsy was not obtained.

CASE 8—S N, a 50 year old white woman, was admitted to the hospital complaining of jaundice of the skin and the scleras coming on after an infection of the upper part of the respiratory tract. She was discharged improved with the diagnosis of toxic hepatitis.

CASE 9—P B, a 70 year old white woman, was admitted to the hospital complaining of pain which had been present in the right upper quadrant of the abdomen and the epigastrium for six weeks. One and a half years previously she had had a similar attack with jaundice and clay-colored stools. The liver was definitely enlarged but not tender. Her course was unfavorable, progressive ascites developed, and she died after twenty-two days in the hospital.

CASE 10—E S, a 58 year old white woman, was admitted to the hospital for the thirteenth time for jaundice, edema of the ankles and anorexia. On the previous admissions a diagnosis of cirrhosis of the liver had been made. The liver and spleen were not felt.

CASE 15—A J, a 35 year old white man, was first admitted to the hospital on Sept 9, 1937, with symptoms of acute cholecystitis. He improved rapidly without operation and was discharged on September 16. He was readmitted on April 25, 1938, with a history of nausea, vomiting, belching and abdominal pain of five days' duration, which had become progressively worse up to the time of admission. His urine had been dark for two days before admission, and jaundice was noted on the day preceding admission. For the preceding five days his temperature had ranged between 101 and 103 F. On admission he appeared acutely ill. His temperature was 103.4 F and his pulse rate 120 per minute. There was jaundice of the skin and the scleras. Tenderness and moderate muscular

Comparative Data in Fifteen Cases of Hepatic Manifestations

Case No	Name	Total Cholesterol, Mg per 100 Cc	Free Cholesterol, %*	Phos phorus, Units	Phos phatase, Units (Bodan sky)	Icterus Index	Van den Bergh Test		Urea Nitrogen, Mg per 100 Cc	Urobilinogen in Urine	Galactose Tolerance Test	Albumin Ratio	Miscellaneous	Diagnosis
							Direct	Indirect Units						
1	E K	315	35	5.6	21	44			110				Uric acid, 12.2 mg per 100 cc	Uremia and hepatitis (confirmed by autopsy)
2†	S B	321	31	6.7	40.1	Clinically jaundiced			43.6					Typhemia of pregnancy (patient died within 48 hr, no autopsy)
3‡	M B	127	32		13.1	20	Biphasic	3.2		1.200	1.26 Gm excreted in 6 hr		Many firm nodules in enlarged liver, revealed at laparotomy	Carcinoma of liver (no primary source found)
4§	F K	290	35		5.3	6.7	Negative	0.81			Normal reaction		Normal reaction to devereux tolerance test	Congenital cysts of liver (revealed at operation)
5	D S	300	20		15	9.8	Delayed	1.08		1.10	Negative		Takata Arn test, negative, negative reaction for tyrosine in urine	Multiple abscesses of liver (confirmed by autopsy), clinically diabetes mellitus
Cases in Which Diagnostic Difficulties Were Presented														
6¶	I A	394	62	3.9	43	66	Biphasic	12.5		1.1	Negative	0.46	Uric acid, 3.7 mg per 100 cc, nonprotein nitrogen, 202 mg per 100 cc, total protein, 8.5 Gm per 100 cc, bromsulphalein test, negative, bile pigments in urine in considerable quantity sedimentation time, 120 mm per hr, fragility test, hemolysis beginning at 0.40 and completed at 0.54	Hepatosplenomegaly of undetermined origin (final diagnosis)
7	L A	257	73.5	4	10	64	Immediate	10.9	7.5				Sugar, 77 mg per 100 cc	Toxic hepatitis
8#	S N	220	75		15	130	Immediate	19	5	At first negative later 1.10	2 Gm excreted within 6 hr	1.84	Bromsulphalein test, 100% retained after 30 min, total protein, 6.6 Gm per 100 cc, fibrinogen, 0.172 Gm per 100 cc, bile pigments in urine, 4+, feces, clay colored, sedimentation time 15 mm per hr	

[illegible]

15	A J	192	43	28	83	71	Biphasic	10 1
<p>* Free cholesterol $\times 100$</p> <p>Total cholesterol</p> <p>† The cholesterol and the urea nitrogen value indicate a fairly well functioning liver. The icterus index indicates some degree of jaundice. The resultant value for serum phosphatase value and the increased urobilinogen in the urine indicate impaired hepatic function. Only some degree of biliary obstruction was present.</p> <p>‡ The low cholesterol value and the relatively slight increase in phosphatase is characteristic of the unaltered functional state of the liver and the slight degree of biliary obstruction were present, therefore, the serum phosphatase was markedly elevated.</p> <p>§ In this case no chemical cholesterol value may have been due to diabetes. The moderate increase in phosphatase is characteristic of the hepatic damage.</p> <p> The slightly elevated cholesterol value indicates a well functioning liver and biliary obstruction was markedly increased. Although marked biliary obstruction of the liver and the tests point to a fairly well functioning liver. A well functioning liver and biliary obstruction was markedly increased. In all these cases, the hepatic function was present.</p> <p>¶ Most of the tests point to a fairly well functioning liver. (The percentage of free cholesterol was markedly elevated. In all these cases, the hepatic function was present.)</p> <p># Almost all the tests in cases 7 and 8 indicate a damaged liver. (The percentage of free cholesterol was markedly elevated. In all these cases, the hepatic function was present.)</p> <p>** The clinical history and biliary obstruction of cases 9 and 10 suggests previous hepatic damage. With only slight jaundice, the serum phosphatase value is characteristic for the degree of hepatic injury and 14 a similar picture for the relatively low value for serum phosphatase even in the presence of marked jaundice.</p> <p>†† In cases 11, 12, 13 and 14 a similar picture for the relatively low value for serum phosphatase even in the presence of marked jaundice.</p>								

spasm were present in the right upper quadrant of the abdomen. The clinical diagnosis was exacerbation of chronic cholecystitis, cholelithiasis and obstructive jaundice. He was prepared for operation by intravenous and subcutaneous administrations of dextrose. Operation with the patient under spinal and general anesthesia was performed approximately thirty hours after admission. The liver was found to be enlarged 2 fingerbreadths below the costal margin and was swollen, edematous, yellow-green, smooth and tense. The gallbladder was small, with omentum wrapped around it. It was edematous and hemorrhagic and contained brown-green bile with small pigmented calculi, one of which was impacted in the cystic duct. The common duct was edematous and thick walled, and calculi were palpable in the common hepatic duct.

The common bile duct contained many small calculi, which were removed. The calculi in the hepatic duct could not be dislodged and removed, because of the edema of the duct. Postoperatively the patient was given a transfusion of whole blood, and fluids were injected intravenously. His condition rapidly became poor, the jaundice increased, and he died approximately twenty-five hours after the operation, with the clinical picture of acute hepatic degeneration (liver death). Preoperative determinations are given in the table.

From the table, it is seen that the serum phosphatase values vary from normal levels to 43 units in cases of hepatocellular jaundice. However, if the underlying state of the hepatic parenchyma is considered in addition to the degree of biliary obstruction, a satisfactory explanation suggests itself. In case 6, in which the listed tests of hepatic function indicate fair functioning of the hepatic parenchyma as well as obstruction in the biliary system, the value for serum phosphatase was 43 units. In this case, both equally important factors are present, namely, good functioning of the hepatic parenchyma and an obstruction. This idea is more clearly brought out when cases 13 and 14 are compared with case 1. In the former, the serum phosphatase never rose to more than 77 units. In these cases severe intrahepatic (hepatocellular) obstruction was evidenced by the clay-colored stools and the quantity of bile pigments in the blood stream. In the cases of acute yellow atrophy in which autopsy was performed the extremely poor condition of the hepatic parenchyma was revealed (figs 1, 2, 3 and 4). Case 1 is another instance of hepatocellular obstruction in which autopsy was performed, but in this case the serum phosphatase values were increased to 21 units. It is true that the patient had much less hepatocellular obstruction, but the hepatic parenchyma was much better preserved. In interpreting the significance of the value of 21 units for serum phosphatase, the role of the two factors mentioned must be considered. Here, therefore, are two examples of hepatitis, with different serum phosphatase values. The explanation lies not only in the degree of obstruction but in the underlying pathologic state of the hepatic parenchyma, i. e., the degree of hepatocellular damage. The serum phosphatase values obtained in cases of severe hepatitis and acute yellow atrophy must therefore not be considered negative results or instances in which this test is valueless. The

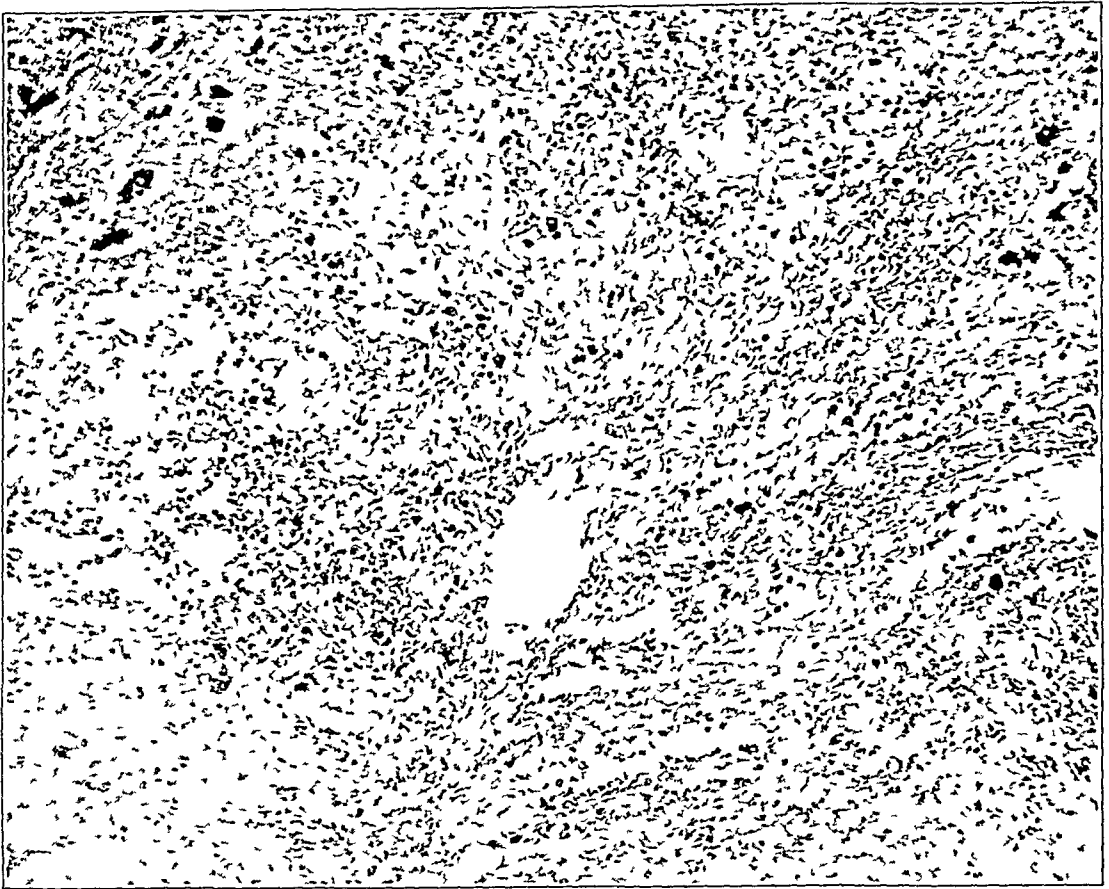


Fig 1 ($\times 160$)—The architecture of the liver is destroyed. The hepatic parenchyma is represented by pink and lavender amorphous material, containing a diffuse scattering of small round cells, some golden-brown pigment granules, large mononuclear cells, a few plasma cells and an occasional polymorphonuclear leukocyte.

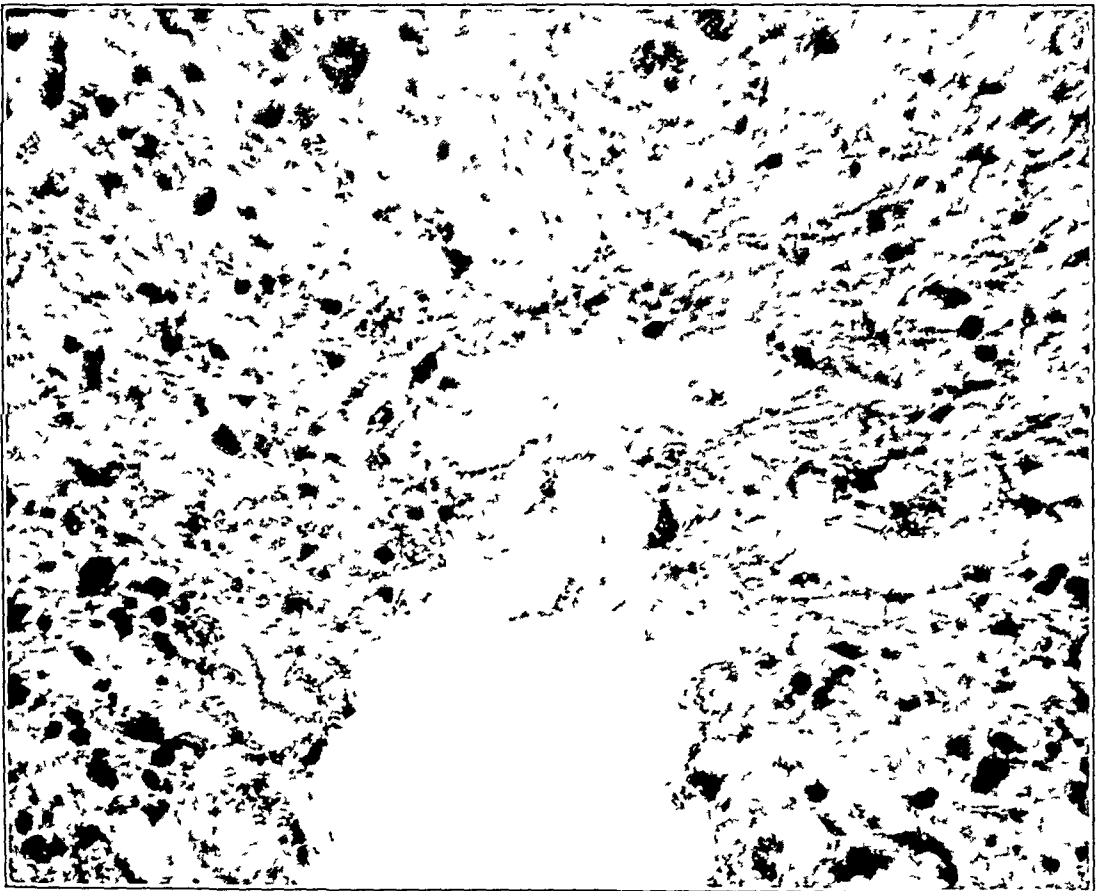


Fig 2 ($\times 711$)—High power magnification of the section shown in figure 1.

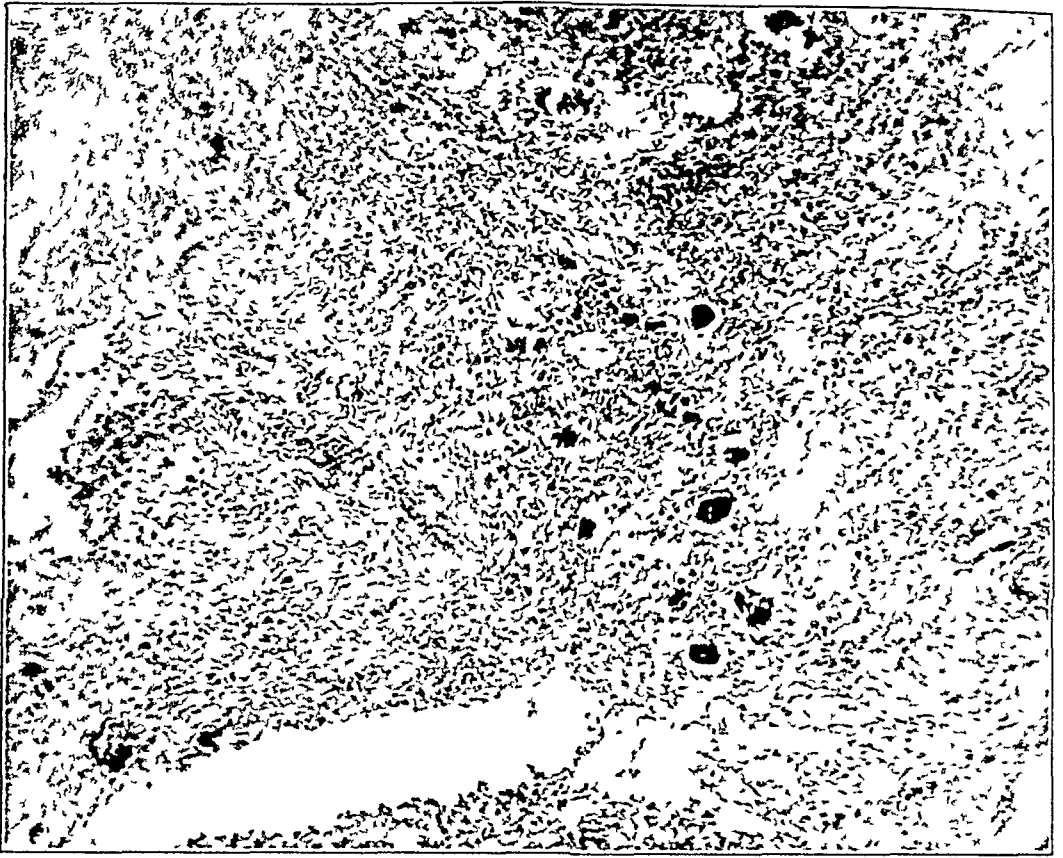


Fig 3 ($\times 160$) —Scattered throughout the tissue is an occasional large liver cell with one or more nuclei

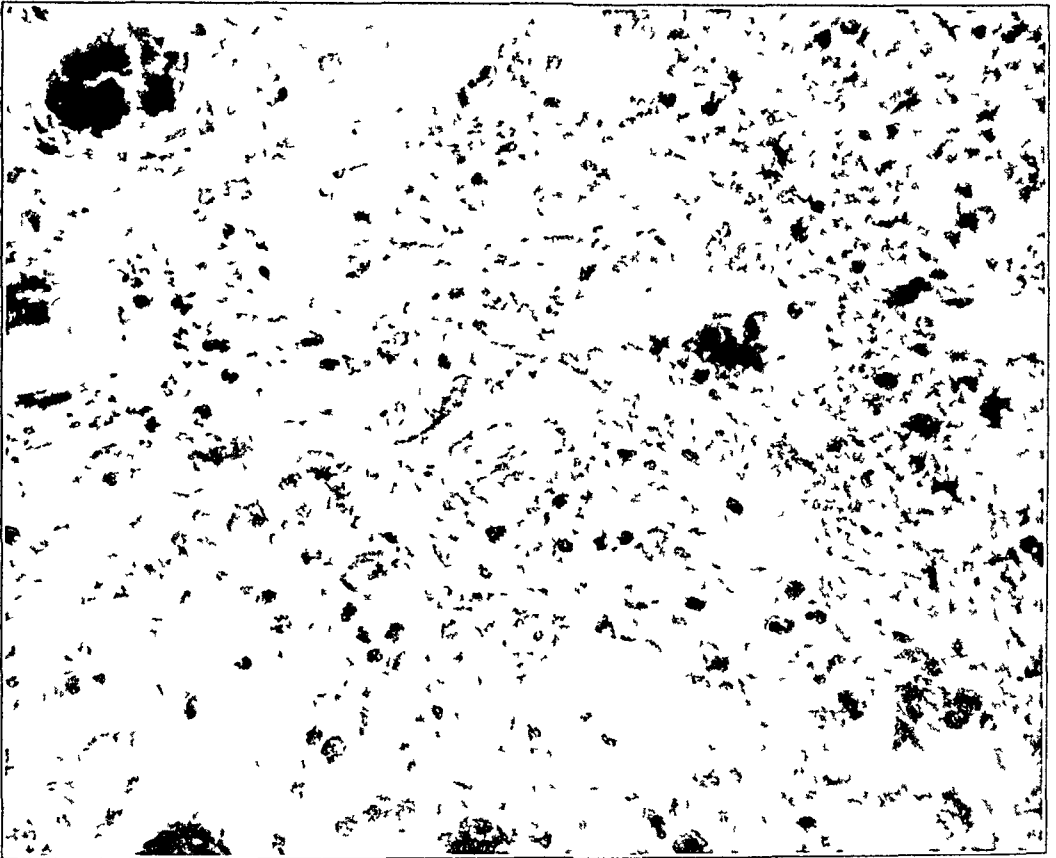


Fig 4 ($\times 711$) —High power magnification of the section shown in figure 3

finding of normal serum phosphatase when a definite biliary obstruction is present should be interpreted along with the other laboratory data, especially the total cholesterol and the ratio of free to total cholesterol in arriving at a conclusion regarding the condition of the hepatic parenchyma

From these statistical studies and the studies of others, especially Cantarow and Nelson,⁵ we have found that it is practically impossible to define the different types of jaundice clearly by characteristic values, those of 10 units or above signifying obstructive jaundice and those below 10 units hepatocellular jaundice. This is especially true for the latter condition, in which the values may vary markedly

From the table one well known fact is brought out clearly, namely, that there is no one adequate test of hepatic function. With the multiplicity of its functions, it is not surprising that the liver can be normal with respect to one function and show abnormalities in another. To interpret each test individually and to correlate its result with the role that the liver plays in the particular function tested will lead to better clinical interpretations and less disappointing results

It is interesting to correlate the values for serum phosphatase with those for cholesterol as an index of the state of the hepatic parenchyma. In cases of extrahepatic obstruction, the rise in serum phosphatase accompanies the rise in total cholesterol, but when the hepatic parenchyma is damaged the total cholesterol, especially the cholesterol ester, is decreased (Epstein and Greenspan²⁰), and the serum phosphatase is normal or only slightly increased even in the presence of an obstruction. This relation and the proper interpretation of serum phosphatase values in clinical cases of jaundice of questionable causation should prove of great value to the clinician and surgeon. The following case is offered as an example

J. M., a 61 year old white man, was admitted to the hospital with a history of progressive jaundice for the past two weeks. Up to that time he had enjoyed excellent health. He then began to have a poor appetite, felt nauseated and vomited. For three days he had had acholic stools. There was no history of pain. Several days prior to admission his jaundice began to decrease, and his stools became darker. On examination, his liver was palpable in the midline and just to the right of the umbilicus, 3 fingerbreadths below the costal margin. There was no tenderness. Carcinoma of the head of the pancreas with obstructive jaundice being suspected, an exploration was performed two days after his admission. The liver was found to be enlarged to the level of the umbilicus, the right lobe more involved than the left. The liver itself was smooth, slate colored and mottled, with no evidence of palpable masses. There was no evidence of extrahepatic obstruction. No other pathologic condition was found in the abdomen. The patient made an uneventful recovery. The case is therefore one of intrahepatic (hepatocellular) jaundice.

20 Epstein, E. Z., and Greenspan, E. B. Clinical Significance of the Cholesterol Partition of the Blood Plasma in Hepatic and in Biliary Diseases, *Arch Int Med* 58 860 (Nov.) 1936

LABORATORY DATA

The urine contained bile pigments and small amounts of urobilinogen. Bile pigments were always present in the feces. Blood determinations on several dates were as follows:

Date	Total Choles terol, Mg per 100 Cc	Free Choles terol, % ²¹	Free Choles terol, Mg per 100 Cc	Phos phorus, Mg per 100 Cc	Icterus Index	Van den Bergh Test		Urea Nitrogen, Mg per 100 Cc	Phos phatase Units (Bo dansky)
						Direct	Indirect, Units		
3/20/38				2.9	101	Biphasic	29.2	16.8	6
	(Operation)								
3/23/38	172	44	76	2.4	172	Biphasic	31		10.4
3/26/38	158	53	83					23.2	
4/ 2/38	139	55	76	3.9	91			16.5	7.6
4/ 9/38	144	40	58		46				
4/16/38	188	30	57	3.3	37				4.8

In this case the cause of jaundice was a problem of differential diagnosis. If it had been a case of extrahepatic obstruction, e. g., carcinoma of the head of the pancreas as suspected, there would have been higher values for total cholesterol and an increase in serum phosphatase. The total cholesterol was at the lower limit of, or slightly below, normality, and there was a marked increase in the percentage of free cholesterol. (The normal values of total cholesterol as determined by the technique employed at the Jewish Hospital of Brooklyn ranges from 160 to 250 mg per hundred cubic centimeters, the percentage of free cholesterol ranging from 24 to 30 per cent.) In four determinations of serum phosphatase the values did not rise above 10.4 units. These findings are characteristic for hepatocellular disease, which laparotomy proved to be present.

With the concept that serum phosphatase values in hepatic and biliary disorders depend on the functional state of the liver cell and the extent of biliary obstruction, an explanation is now offered for the paradoxical results in three types of cases.

To explain the rise in serum phosphatase in cases of cholecystitis, we refer to the degree of biliary obstruction. To quote Charles H. Mayo²²: "In cholelithiasis the formation of gallstones is not primary, but there is first biliary tension, next hepatitis or grades of cholangitis, and third, cholecystitis." The slight amount of biliary obstruction from the developing cholangitis is enough to cause a rise in serum phosphatase but not in the icterus index. It has been shown¹⁹ that obstruction of only one seventh, approximately, of the biliary system of a dog will cause more than a tenfold rise in serum phosphatase but no accumulation of the bile pigments.

²¹ $\frac{\text{Free cholesterol} \times 100}{\text{Total cholesterol}}$

²² Mayo, C. H. Unappreciated Hepatic Function, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2.

In cases of congenital anomalies of the bile ducts in newborn infants, the rise in the icterus index is readily accounted for. Microscopic examination of the livers in such cases reveals the varying degrees of degeneration. Therefore, even though there is an extrahepatic obstruction, the rise in serum phosphatase does not follow, because of the equally important factor, namely, the poor functional state of the liver cell.

In cases of cirrhosis of the liver, the serum phosphatase values vary from normal to 21 units. This may be accounted for by the different degrees of hepatic damage and biliary obstruction that exist in these conditions.

In some cases of extrahepatic obstruction (jaundice caused by a biliary calculus), the values of serum phosphatase often change, depending on the degree of obstruction. In the third type of case, exemplified by case 15 in the table, there evidently is some degree of obstruction. Phosphatase values do not decrease as quickly as the icterus index when the obstruction is released, as proved clinically and experimentally by Armstrong and King¹¹. In case 15 the patient had had several attacks of cholangitis previously, and his hepatic parenchyma was probably damaged. This kind of hepatic condition may be the type that predisposes to liver death, as noticed by Graham²³. The normal or only slightly increased phosphatase value in the presence of a high icterus index, with a clinical story of extrahepatic obstruction, leads one to believe that in this case, although a certain degree of obstruction was present, the poor state of the liver cell prevented more than a slight increase in serum phosphatase and was the underlying cause of the rapid death. Unfortunately permission for autopsy was not obtained.

CONCLUSION

- 1 In cases of hepatocellular jaundice with obstruction, serum phosphatase values remain normal or increase slightly if the hepatic parenchyma is severely damaged.

- 2 In cases of hepatocellular jaundice in which obstruction is definitely present and the hepatic parenchyma is in a good functional state, serum phosphatase values are markedly increased. The amount of increase is not clearly characteristic but depends on two factors: (a) the functional state of the liver cell and (b) the extent of biliary obstruction.

- 3 Serum phosphatase values are a valuable aid in the differential diagnosis of jaundice. These values must be interpreted along with other hepatic tests to reveal the metabolic and functional state of the hepatic parenchyma and the patency of the biliary channels.

²³ Graham, E. A. Lowering Mortality After Operations on the Biliary Tract, *Illinois M. J.* **60** 196, 1931.

Progress in Internal Medicine

INFECTIOUS DISEASES

HOBART A REIMANN, M D

PHILADELPHIA

In the field of infectious diseases during the past year chemotherapy demanded the most attention. Notable advances in knowledge were made also with respect to the relationship between certain infectious diseases of animals and those of man, to which considerable space has been given in this review. Perhaps the most interesting and important single contribution was the discovery of an enzyme in bacilli found in the soil which actually destroys gram-positive cocci in the test tube and in the animal body.

SULFANILAMIDE AND SULFAPYRIDINE (2 [PARAAMINOBENZENE SULFONAMIDO] PYRIDINE) IN THE TREATMENT OF VARIOUS INFECTIONS

Limitation of space permits only a brief résumé of the subject. Lest this become a review of reviews, the reader is referred to a number of general papers and monographs on sulfanilamide and related compounds.¹

American² and British³ investigators strengthened the view previously held that sulfanilamide exerts its beneficial effect in certain infectious diseases by limiting or preventing the growth of bacteria, thus permitting the body to develop its own immune mechanism to overcome infection. There is no evidence to show that increased action

1 (a) Holman, W L, and Duff, G L. Sulfanilamide and Similar Compounds in Chemotherapy, *Am J M Sc* **195** 379-416 (March) 1938. (b) Whitby, L. Chemotherapy of Bacterial Infections, *Lancet* **2** 1095-1103 (Nov 12) 1938. (c) Long, P H, and Bliss, E A. The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939. (d) Mellon, R R, and Gross, P. Sulfanilamide Therapy of Bacterial Infections with Special Reference to Diseases Caused by Hemolytic Streptococcus, Pneumococci, Meningococci and Gonococci, Springfield, Ill, Charles C Thomas, Publisher, 1938. (e) Marshall, E K. Bacterial Chemotherapy. The Pharmacology of Sulfapyridine, *Physiol Rev* **19** 240-269 (April) 1939.

2 Long, P H, Bliss, E A, and Feinstein, W H. Mode of Action, Clinical Use and Toxic Manifestations of Sulfanilamide, *J A M A* **112** 115-121 (Jan 14) 1939.

3 McIntosh, J, and Whitby, L. The Mode of Action of Drugs of the Sulphonamide Group, *Lancet* **1** 431-435 (Feb 25) 1939.

of phagocytic cells, neutralization of toxins or direct effect on the bacterial cell body or capsule takes place. Bacteriostasis is presumably brought about by some interference with the nutrition of the bacterial body which prevents growth or multiplication.

Shaffer ^{3a} advances evidence to show that sulfanilamide and sulfapyridine exert their therapeutic and toxic effects through oxidation products formed by the action of atmospheric oxygen on these substances under the catalytic influence of respiring tissues or organisms. Other work ^{3b} shows that pneumococci which become "sulfapyridine-fast" suffer a loss of dehydrogenase activity against certain carbon compounds.

A new compound, sulfapyridine, was introduced ⁴ in 1938 as an agent more effective than sulfanilamide against pneumococcal infections in mice. It was also supposedly less toxic for the patient than sulfanilamide, but the work of Marshall and co-workers ⁵ does not support this view. Until more is known about the drug, it should not be used in conditions for which sulfanilamide is effective.

Workers in general who intend to publish observations on the therapeutic effects of any sulfanilamide compounds should read the critical comments of Marshall ⁶ and of others ⁷ on the indiscriminate use of newly introduced drugs.

Pneumococcal Infections—Interest stimulated by reports from England as to the greater effectiveness of sulfapyridine as compared with sulfanilamide against pneumococcal infection in mice has led to widespread use of the drug in the treatment of patients with pneumonia and meningitis, although knowledge of its effectiveness in these composite diseases has not yet been established. In many cases the drug is given on the first appearance of any infection of the respiratory tract. If this custom becomes general, much harm will follow. Uncontrolled and careless use of any valuable drug injures its reputation. Sulfapyridine properly used is valuable in the treatment of patients whose pneumonia or meningitis is caused by the pneumococcus and should be

3a Shaffer, P. A. The Mode of Action of Sulphanilamide, *Science* **89** 547-550 (June 16) 1939.

3b MacLeod, C. M. Metabolism of "Sulfapyridine-Fast" and Parent Strains of *Pneumococcus* Type I, *Proc Soc Exper Biol & Med* **41** 215-218 (May) 1939.

4 Whitby, L. E. H. Chemotherapy of Pneumococcal and Other Infections with 2(p-Aminobenzenesulfonamido) Pyridine, *Lancet* **1** 1210-1211 (May 28) 1938.

5 Marshall, E. K., Bratton, A. C., and Litchfield, J. T. The Toxicity and Absorption of 2-Sulfanilamidopyridine and Its Soluble Sodium Salt, *Science* **88** 597-599 (Dec 23) 1938.

6 Marshall, E. K. An Unfortunate Situation in the Field of Bacterial Chemotherapy, *J A M A* **112** 352-353 (Jan 28) 1939.

7 Bullowa, J. G. M., Plummer, N., and Finland, M. Sulfapyridine in the Treatment of Pneumonia, *J A M A* **112** 570 (Feb 11) 1939.

used at present only in cases of infection caused by this bacterium. In my experience it has seemed to be harmful in cases of an atypical form of pneumonia to be described later. It may be argued that it should be used in all cases of acute pulmonary infection as a measure preventive of possible invasion by the pneumococcus, but no evidence is as yet available to support adoption of this plan. It is still of great importance, therefore, to make an etiologic diagnosis of pneumonia in every case before using chemotherapy.

A number of investigators have attempted to explain the mechanism of the beneficial action of the drug. It was thought at first to have some destructive effect on the capsule of the pneumococcus or to reduce the virulence of the organism. Neither of these views has received support. As in the case of other bacteria, bacteriostasis seems to afford the most likely explanation. British observers⁸ claim that different strains of pneumococci vary greatly in sensitivity to sulfapyridine and recommend the use of tests to discover whether the pneumococcus to be dealt with in a patient is sensitive or not. Pneumococci, they believe, may become "fast" or resistant to sulfapyridine in the body. Such fastness, resistance or tolerance to drugs or chemicals apparently may be developed in the test tube,^{8a} but I have never been convinced of its occurrence in the body. Sulfapyridine, they found, was more effective in animals previously vaccinated against the specific type of *Pneumococcus* used. Other observers⁹ had more success in treating rats when both sulfapyridine and specific immune serum were used than when either was used alone. After infection was well established, serum was more effective than the drug. Sulfapyridine had but little curative effect on lesions in mice caused by pneumococci of types II, III and VIII¹⁰. Sulfapyridine does not represent the ultimate goal in chemotherapy of pneumococcic infections¹¹.

Pneumococcic Pneumonia. Early indications of the effectiveness of sulfapyridine against several types of *Pneumococcus* led to the hope

8 Maclean, I. H., Rogers, K. B., and Fleming, A. M. & B. 693 and Pneumonia. *Lancet* **1** 562-568 (March 11) 1939.

8a MacLeod, C. M., and Daddi, G. A. "Sulfapyridine-Fast" Strain of *Pneumococcus* Type I, *Proc Soc Exper Biol & Med* **41** 69-71 (May) 1939.

9 Kepl, M., and Gunn, F. D. Sulfapyridine and Serum Therapy in Experimental Lobar Pneumonia of Rats, *Proc Soc Exper Biol & Med* **40** 529-532 (April) 1939.

10 Schmidt, L. H., and Hilles, C. Further Studies on Therapeutic Properties of Sulfapyridine in Experimental *Pneumococcus* Infections, *Proc Soc Exper Biol & Med* **40** 611-614 (April) 1939.

11 Bliss, E. A., Feinstein, W. H., Garrett, A. W., and Long, P. H. Sulfapyridine and Sulfanilamide in Experimental *Pneumococcal*, *Meningococcal*, *Welch Bacillary* and *Friedlander's Bacillary* Infections in Mice, *Proc Soc Exper Biol & Med* **40** 619-621 (April) 1939.

that it would be useful in treating patients with pneumococcic pneumonia, without typing. This hope at present is certainly not justified.

A series of papers published after the one of Evans and Gaisford¹² uniformly show a striking reduction of the duration of illness and of the mortality in cases of pneumococcic pneumonia following treatment with sulfapyridine. All of them, however, deal with observations made in a single season (1938-1939) and in all a death rate of 4 to 8 per cent is reported.¹³ It may be remarked here that other observers noted a death rate of 3.3 per cent in patients treated with specific immune serum alone. According to many physicians, pneumonia in the winter of 1938-1939 was "mild." This suggests only that the prevalence of pneumonia due to *Pneumococcus* types I, II, III, V and VIII was not as great in certain places as in other years. Furthermore, numerous epidemics of a mild form of pneumonia, apparently not caused by bacteria, occurred in many parts of the country (page 380). Many persons with this form of pneumonia harbored pneumococci in the nasopharynx, as carriers. These pneumococci, which were usually of the higher-numbered types, were found when the sputum was typed. They were often mistaken for the causative agent of the disease, and sulfapyridine was given needlessly. It is highly probable that cases of this form of

12 Evans, G. M., and Gaisford, W. F. Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine, *Lancet* **2** 14-19 (July 2) 1938.

13 (a) Dyke, S. C., and Reid, G. C. K. Treatment of Lobar Pneumonia with M & B 693, *Lancet* **2** 1157-1160 (Nov. 19) 1938. (b) Williams, R. B., and Lawson, G. B. Graphic Evidence of Response with Sulfanilamide in Pneumonia and Pneumococcal Infections, *Virginia M. Monthly* **65** 727-732 (Dec.) 1938. (c) Flippin, H. F., Lockwood, J. S., Pepper, D. S., and Schwartz, S. The Treatment of Pneumococcic Pneumonia with Sulfapyridine, *J. A. M. A.* **112** 529-534 (Feb. 11) 1939. (d) Wilson, A. T., Spreen, A. H., Cooper, M. L., Stevenson, F. E., Cullem, G. E., and Mitchell, A. G. Sulfapyridine in Pneumonia, *ibid.* **112** 1435-1439 (April 15) 1939. (e) Barnett, H. L., Hartmann, A. F., Perley, A. M., and Ruhoff, M. B. The Treatment of Pneumococcic Infections in Infants and Children with Sulfapyridine, *ibid.* **112** 518-527 (Feb. 11) 1939. (f) Sadusk, J. F. Observations on Sulfanilamide Therapy in Pneumonia and Meningitis Due to Type III Pneumococci, *New England J. Med.* **219** 787-790 (Nov. 17) 1938. (g) Anderson, T. T., and Dowdeswell, R. M. Treatment of Pneumonia with M & B 693, *Lancet* **1** 252-254 (Feb. 4) 1939. (h) Agranat, A. L., Dreosti, A. O., and Ordman, D. Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine (M & B 693), *ibid.* **1** 309-317 (Feb. 11), 380-384 (Feb. 18) 1939. (i) Price, A. E., and Myers, G. B. Treatment of Pneumococcic Pneumonia with Sulfanilamide, *J. A. M. A.* **112** 1021-1027 (March 18) 1939. (j) Hodes, H. L., Stifler, W. C., Walker, E., McCarty, M., and Shirley, R. G. The Use of Sulfapyridine in Primary Pneumococcic Pneumonia and in Pneumococcic Pneumonia Associated with Measles, *J. Pediat.* **14** 417-446 (April) 1939. (k) Finland, M., Spring, W. C., Jr., Lowell, F. C., and Brown, J. W. Specific Serotherapy and Chemotherapy of the Pneumococcic Pneumonias, *Ann. Int. Med.* **12**. 1816-1829 (May) 1939.

pneumonia were often included in statistics that were reported as showing the beneficial effects of chemotherapy. The presence of pneumococci or other bacteria in the sputum does not always indicate that these organisms have etiologic significance.

According to authoritative opinion,¹⁴ it seems wisest at present to treat pneumococcic pneumonia with both specific immune serum and sulfapyridine. Generally speaking, when a diagnosis of pneumococcic pneumonia is reasonably certain, and after specimens of blood have been taken for making cultures and cell counts, the patient should be given 2 to 4 Gm of sulfapyridine while the type of pneumococcus is being determined. When the type is known, specific immune serum and sulfapyridine may then be given together. To patients who for various reasons cannot be given serum the drug may be given alone, and, of course, the reverse applies. The objection to the insolubility of the compound now used may be overcome by use of its sodium salt,¹⁵ but nausea and vomiting still occur, presumably because of an effect of the drug on the central nervous system. While combined use of the serum and drug seems to be advisable now, it is unfortunate for statistical reasons, since the true value of sulfapyridine will be obscured unless the drug is used alone. Before the value of sulfapyridine will finally be known, it will be necessary to use it alone in the treatment of large numbers of patients with pneumococcic pneumonia with particular respect to the type of *Pneumococcus*, the age of the patient, the presence of other diseases or complications, the presence or absence of bacteremia and the day on which treatment was begun.

Another interesting and important agent capable of attacking pneumococci was discovered by Dubos, whose paper, published during the height of enthusiasm for chemotherapy, received scant attention.¹⁵ He isolated from soil an unidentified spore-bearing bacillus which after it has grown in soil to which suspensions of various gram-positive cocci have been added over a long period forms an enzyme capable of dissolving these cocci. Pneumococci, staphylococci, hemolytic or green-producing streptococci and indifferent streptococci are all susceptible. Besides killing these bacteria when incubated with them in vitro, the bacterial extract injected in minute amounts intraperitoneally into mice protects them against 100,000 fatal doses of pneumococci of types I, II, III, V and VIII. The extract exerts a curative effect also when injected several hours after inoculation of these cocci. It is different from the enzyme previously discovered by Dubos and Avery, which attacks only the polysaccharide capsule of the type III pneumococcus.

14 Marshall, E. K., and Long, P. H. The Intravenous Use of Sodium Sulfapyridine, *J. A. M. A.* **112** 1671-1675 (April 29) 1939.

15 Dubos, R. J. Bactericidal Effect of an Extract of a Soil Bacillus on Gram Positive Cocci, *Proc. Soc. Exper. Biol. & Med.* **40** 311-312 (Feb.) 1939.

and which never had a successful clinical trial. The new extract kills gram-positive cocci but is without effect on gram-negative ones or on gram-negative bacilli. Its effect on infections in man has not yet been reported, but one may predict that it will be useful if it works as well in the patient as it does in mice. If the substance can be standardized and if it is nontoxic, it may even supersede antiserum and sulfapyridine.

Pneumococcic Meningitis. The effectiveness of sulfanilamide and sulfapyridine is more striking in pneumococcic meningitis¹⁶ than in pneumococcic pneumonia, but here again many published reports deal with isolated cases rather than with controlled series of cases. Nevertheless, the number of cases now on record in which recovery followed treatment of this infection, which when untreated is usually regarded as fatal in over 95 per cent of the cases, warrants the use of the drug. Experimental studies in mice showed that 73 per cent of treated animals recovered, as compared with 100 per cent that died in an untreated series.¹⁷

Finland, Brown and Rauh¹⁸ recommend frequent complete drainage of spinal fluid, immediate and continuous use of sulfanilamide with sodium bicarbonate, identification of the type of *Pneumococcus*, intravenous administration of specific antipneumococcus serum until the concentration of immune body in the blood is sufficient, moderate intake of fluid, and intraspinal injection of 5 or 10 cc. of the patient's own serum. The last procedure, recommended as a means of adding to complement, is based on the earlier work of Fothergill in combating meningitis due to the influenza bacillus, but it seems to me to be more theoretic than practical. If anemia results from sulfanilamide, transfusion of blood is advised. Of 10 patients treated, 6 recovered—a noteworthy fact, indeed.

References to many recently published papers on the treatment of pneumococcic meningitis with sulfanilamide may be found in a review by Holman and Duff.¹⁹

16 (a) Reid, G. C. K., and Dyke, S. C. Pneumococcic Meningitis Treated with 2-(p-Aminobenzenesulphonamido) Pyridine, *Lancet* **2** 619-620 (Sept. 10) 1938. (b) Neal, J. B. The Treatment of Acute Infections of the Central Nervous System with Sulfanilamide, *J. A. M. A.* **111** 1353-1356 (Oct. 8) 1938. (c) Hewell, B. A., and Mitchell, A. G. The Treatment of Pneumococcic Meningitis with Sulfanilamide. Review of Literature and Report of Six Additional Cases, *ibid.* **112** 1033-1037 (March 18) 1939.

17 Cooper, F. B., Gross, P., and Lewis, M. Chemotherapy of Pneumococcal (Type II) Meningitis in the Rat, *Proc. Soc. Exper. Biol. & Med.* **38** 835-836 (June) 1938.

18 Finland, M., Brown, J. W., and Rauh, A. E. Treatment of Pneumococcic Meningitis. A Study of Ten Cases Treated with Sulfanilamide Alone or in Various Combinations with Specific Antipneumococcic Serum and Complement, Including Six Recoveries, *New England J. Med.* **218** 1033-1044 (June 23) 1938.

In the experience of Hewell and Mitchell^{16c} all of 23 children with pneumococcic meningitis treated before 1937 died, with the use of sulfanilamide 4 of 7 patients have recovered. According to their data, there are now reported more than 30 recoveries which followed treatment with sulfanilamide, but in some cases the dose was so small as to render its effectiveness doubtful. At least 9 cases have been reported in which the drug was ineffective, there was bacteremia in 7 of these. These authors review the literature on the subject.

Although no extensive studies of the use of sulfanilamide or sulfapyridine in the treatment of pneumococcic empyema have been reported, it is felt that such treatment is not particularly effective in this condition. Two of my patients had 7 and 17 mg of sulfapyridine per hundred cubic centimeters of pleural exudate, yet no benefit was apparent. It is curious that the drug should act so well in pneumococcic meningitis and apparently not in empyema.

Rueggsegger's¹⁹ patients with pneumococcic endocarditis all succumbed even though a concentration of 8 to 17 mg per hundred cubic centimeters of sulfanilamide was present in the blood.

Streptococcic Infections—According to Chandler and Janeway,²⁰ growing hemolytic streptococci in dilute sulfanilamide broth does not cause attenuation of these bacteria. Phagocytosis is promoted, but apparently only as a consequence of the toxic effect of the drug on the bacteria and not as a result of any direct effect on phagocytes. Probably a loose union of the drug with the bacterial bodies occurs. The presence of specific antibody greatly increases the bacteriostatic and bactericidal effect of sulfanilamide. Other workers²¹ in the same laboratory found that an elevation in electrode potential accompanied sulfanilamide bacteriostasis and that a rapid fall in potential accompanied normal growth. Yet others²² found that the oxidation-reduction potential was elevated. (See discussion beginning on page 362 and footnotes 3a and 3b.)

Reports have been made of single cases of recovery from meningitis due to the hemolytic streptococcus, after treatment with sulfanilamide. Favorable reports continue to appear about the effect of this therapy on

19 Rueggsegger, J. M. Pneumococcic Endocarditis, *Arch Int Med* **62** 388-400 (Sept) 1938.

20 Chandler, C. A., and Janeway, C. A. Observations on the Mode of Action of Sulfanilamide in Vitro, *Proc Soc Exper Biol & Med* **40** 179-184 (Feb) 1939.

21 Fox, C. L., German, B., and Janeway, C. A. Effect of Sulfanilamide on Electrode Potential of Hemolytic Streptococcal Cultures, *Proc Soc Exper Biol & Med* **40** 184-189 (Feb) 1939.

22 Warren, J., Street, J. A., and Stokinger, H. E. Influence of Sulfanilamide and Related Compounds upon Oxidation-Reduction Potentials of Hemolytic Streptococcus, *Proc Soc Exper Biol & Med* **40** 208-212 (Feb) 1939.

erysipelas Scarlet fever, on the other hand, is not influenced much In series of cases reported by Sako, Dwan and Platou²³ complications were much less frequent among patients treated with sulfanilamide Sulfanilamide seemed to be of value in preventing the development of scarlet fever in a number of boys exposed to infection These authors believe that early intravenous injection of massive doses of serum to combat toxemia together with administration of large doses of sulfanilamide seems to be the best method of treatment for scarlet fever According to Wesselhoeft and Smith,²⁴ sulfanilamide does not reduce the toxicity or the duration of scarlet fever It had no influence in reducing the number of complications unless given over a long period The drug failed to reduce the number of carriers among convalescent patients

Coburn and Moore²⁵ gave sulfanilamide to guinea pigs suffering from abscesses induced by hemolytic streptococci The abscesses were not sterilized, but when the drug was given either prophylactically or therapeutically cervical adenitis and spontaneous infections were prevented in the treated as compared with the untreated animals In clinical experiments sulfanilamide given after the onset of incidental streptococcal infection of the throat in patients who had had rheumatic fever did not prevent recrudescence of rheumatic fever, however, when the drug was given to 80 rheumatic children prophylactically, 79 of these children escaped incidental infection with hemolytic streptococci and rheumatic activity Other work also suggests the prophylactic value of the drug²⁶

Goodman²⁷ reports 4 cases of a peculiar, previously undescribed form of primary ulcer of skin apparently caused by hemolytic streptococci Three patients treated with sulfanilamide recovered promptly Major and Leger²⁸ report the case of a patient with subacute bacterial

23 Sako, W, Dwan, P F, and Platou, E S Sulfanilamide and Serum in the Treatment and Prophylaxis of Scarlet Fever, *J A M A* **111** 995-997 (Sept 10) 1938

24 Wesselhoeft, C, and Smith, E C The Use of Sulfanilamide in Scarlet Fever, *New England J Med* **219** 947-952 (Dec 15) 1938

25 Coburn, A F, and Moore, L V The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infection with Especial Reference to Rheumatic Fever, *J Clin Investigation* **18** 147-155 (Jan) 1939

26 Thomas, C B, and France, R A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull Johns Hopkins Hosp* **64** 67-77 (Jan) 1939 Hoare, E D The Case for Prophylaxis with Sulfanilamide and Sulfapyridine, *Lancet* **1** 76-79 (Jan 14) 1939

27 Goodman, M H Chronic Streptococcal Ulcer of the Skin Unresponsive to Local Therapy but Cured by Sulfanilamide Report of Two Cases, *J A M A* **111** 1427-1431 (Oct 15) 1938

28 Major, R H, and Leger, L H Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, *J A M A* **111** 1919-1920 (Nov 19) 1938

endocarditis who was apparently cured by sulfanilamide therapy. The patient died of heart failure twenty-nine days after the temperature had been reduced to normal. The blood became sterile about ten days after the administration of sulfanilamide was begun, and the temperature became normal three days later. At necropsy gram-positive cocci were seen in the leaflets of the aortic valve, but cultures were sterile. I have been informed of several other patients with the disease who were similarly treated but with discouraging results, and in my own experience the temperature of several treated patients was temporarily reduced without other beneficial effects. A similar report is made by Ellis²⁹

Meningococcic Meningitis—Reports of the effectiveness of sulfanilamide in the treatment of meningococcic infections are uniformly favorable. Numerous papers on the subject are referred to by Whitby^{1b}. A paper by Banks³⁰ is especially valuable. He believes that while combined sulfanilamide and immune serum therapy is valuable, treatment with sulfanilamide alone is just as good. Of 16 patients so treated, 15 recovered. The mortality rate in 59 patients treated with serum and drugs was 11.8 per cent. A similar optimistic report is published by Waghelstein³¹. Among 106 patients the mortality rate in those who were adequately treated was 12 per cent.

Gonococcic Infections—The effect of sulfanilamide and its compounds on gonorrhea has not been observed long enough to establish the value of these agents as permanently curative or as eliminating gonococci from the entire system. Almost all clinical reports indicate that the effects of treatment are beneficial, especially if treatment is delayed until the primary acute stage has passed³². McGregor-

29 Ellis, G. R. Treatment of Subacute Bacterial Endocarditis with Sulfapyridine, *Lancet* **2** 1521-1522 (Dec. 31) 1938.

30 Banks, H. S. Serum and Sulfanilamide in Acute Meningococcal Meningitis, *Lancet* **2** 7-13 (July 2) 1938.

31 Waghelstein, J. M. Sulfanilamide in the Treatment of One Hundred Patients with Meningococcic Infection, *J. A. M. A.* **111** 2172-2174 (Dec. 10) 1938.

32 (a) Bowie, F. J. T. Chemotherapy in Gonorrhea. Preliminary Report on the Use of 2-(p-Aminobenzenesulphonamido) Pyridine, *Brit. M. J.* **2** 283-284 (Aug. 6) 1938. (b) Felke, H. Chemotherapy of Gonorrhea with Sulfanilamide Compounds Particularly with Diseptal C (D. B. 32), *Arch. f. Dermat. u. Syph.* **178** 45-53 (Aug. 20) 1938. (c) McGregor-Robertson, G. J. Acute Gonorrhea Treated with M. & B. 693. Report on One Hundred Cases, *Lancet* **2** 1463-1465 (Dec. 24) 1938. (d) Cokkinis, A. J., and McElligott, G. L. M. Sulfanilamide in Gonorrhea. Analysis of Six Hundred and Thirty-Three Cases, *ibid.* **2** 355-361 (Aug. 13) 1938. (e) Lloyd, V. E., Erskine, D., and Johnson, A. G. Chemotherapy of Gonorrhea with M. & B. 693, *ibid.* **2** 1160-1163 (Nov. 19) 1938. (f) Prebble, E. E. Treatment of Acute Gonorrhea with M. & B. 693, *ibid.* **2** 1163-

Robertson^{32c} reports success in treating 100 patients with sultapyridine and advises against delay in starting treatment. Most observers agree that the greatest good is accomplished by rest in bed during the treatment with the drug. Treatment of ambulatory patients is generally not recommended. Relapse after clinical cure is fairly common. Although certain observers^{32g} admit that the mortality from the use of sulfanilamide may be higher than that from gonorrhea alone, they strongly urge the use of the drug. In untreated patients the carrier state may persist for several months, these authors believe it is considerably shortened after treatment with sulfanilamide. Patients with gonorrheal ophthalmia also appeared to be helped by the drug³³.

Carpenter and his associates³⁴ present evidence that when sulfanilamide is injected with gonococcus "toxin" into mice it protects the mice from death.

Undulant Fever—Fifteen or more papers have been published during the year on the use of sulfanilamide in the treatment of brucellosis. Most of them cite favorable effects of the drug in single cases, which in view of the frequent spontaneous remissions of the disease are of little value as evidence. In a number of published charts it seems indicated that the temperature was falling before the drug was given. Neumann³⁵ reports favorable effects in 20 cases. In 4 cases studied by Welch, Wentworth and Mickle³⁶ the effect of sulfanilamide in influencing the course of infection was doubtful. They paid much more attention to the effect on the opsonocytophagic index, which seems to me to be of little importance. Bynum³⁷ was unable to duplicate the satisfactory results obtained by others. The drug, given in adequate doses, did not influence the course in 6 of his cases.

1164 (Nov 19) 1938, (g) Silver, B, and Elliott, M. The Use of Sulfanilamide in One Thousand Six Hundred and Twenty-Five Cases of Gonorrhea in the Male, *J A M A* **112** 723-728 (Feb 25) 1939. (h) Ferguson, C, Buchholtz, M, and Gromet, R Y. Sulfanilamide Therapy in Gonorrhea. Review of Literature and Report of 298 Cases, *Am J M Sc* **197** 452-464 (April) 1939.

33 Fernandez, L J, and Fernandez, R F. Sulfanilamide in Gonorrheal Ophthalmia. Preliminary Report, *Am J Ophth* **21** 763-766 (July) 1938.

34 Carpenter, C M, Hawley, P L, and Barbour, G M. The Protective Action of Sulfanilamide in Mice Against Gonococcal "Toxin," *Science* **88** 530-531 (Dec 2) 1938.

35 Neumann, C Z. Treatment of Undulant Fever with Prontosil, *Brit M J* **2** 342-343 (Aug 13) 1938.

36 Welch, H, Wentworth, J A, and Mickle, F L. The Use of Sulfanilamide in the Diagnosis and Treatment of Brucellosis, *J A M A* **111** 226-237 (July 16) 1938.

37 Bynum, W T. Recurrences of Undulant Fever (Brucellosis) Following the Administration of Sulfanilamide, *J A M A* **112** 835-836 (March 4) 1939.

Debono³⁸ used sulfanilamide and the original prontosil (the hydrochloride of 4-sulfamido-2'-4'-diaminoazobenzene) in the treatment of 25 patients suffering from an infection with *Brucella melitensis* in Malta. In no case could recovery be attributed without doubt to these drugs. He does not feel that chemotherapy, with its element of danger, is justified in cases of brucellosis. Other physicians in Malta obtained better results. It is obvious that enough information is not as yet at hand to enable one to judge the value of sulfanilamide in the treatment of patients with undulant fever. More valuable information, it seems, could be obtained from controlled experiments in animals, but in the few papers on experimental results published last year³⁹ it is indicated that only a few animals were used in each investigation—far too few to be of significance. Chinn^{39a} treated only 6 infected guinea pigs and decided that the drug is effective in preventing generalized infection. In a later paper^{39b} the evidence is more convincing, but positive results were obtained only when the drug was given immediately after infection. Menefee and Poston^{39c} showed that sulfanilamide exerts a bacteriostatic action on brucellas inoculated into guinea pigs, especially in the presence of immune bodies.

Miscellaneous Infections—A number of investigators⁴⁰ find sulfanilamide to be of value in the treatment of venereal lymphogranuloma, a disease caused by a filterable virus, although the permanency of the "cure" is uncertain. Similar beneficial effects were noted in experimentally infected mice.

There seems to be a difference of opinion as to the effectiveness of sulfanilamide compounds in experimental tuberculosis⁴¹. According to

38 Debono, J. E. Treatment of *Brucella Melitensis* Infection with Prontosil, *Brit M J* **1** 326-327 (Feb 18) 1939

39 (a) Chinn, B. D. In Vitro and in Vivo Effect of Sulfanilamide on *Brucella Abortus* and *Brucella Suis*, *Proc Soc Exper Biol & Med* **38** 732-734 (June) 1938, (b) The Use of Sulfanilamide in Experimental Brucellosis, *J Infect Dis* **64** 78-82 (Jan-Feb) 1939. (c) Wilson, G. S., and Maier, I. The Sulphanilamide Treatment of Guinea Pigs Infected with *Brucella Abortus*, *Brit M J* **1** 8-10 (Jan 7) 1939. (d) Menefee, E. E., and Poston, M. A. Effects of Sulfanilamide on *Brucella Melitensis*, var *Melitensis*, *Abortus* and *Suis*, *J Bact* **37** 269-276 (March) 1939.

40 Shropshire, G. Sulfanilamide in Treatment of Strictures of the Rectum Caused by Lymphogranuloma Venereum, *Illinois M J* **74** 153-161 (Aug) 1938. Shaffer, L. W., and Arnold, E. Lymphogranuloma Venereum, Especially Its Treatment with Sulfanilamide, *Arch f Dermat u Syph* **38** 705-712 (Nov) 1938. MacCallum, F. O., and Findlay, G. M. Chemotherapeutic Experiments on Virus of Venereal Lymphogranuloma, *Lancet* **2** 136 (July 16) 1938. Knight, A. A., and David, V. C. The Treatment of Venereal Lymphogranuloma with Sulfanilamide, *J A M A* **112** 527-529 (Feb 11) 1939.

41 Greev, P. H., Baddington, G. D. M., and Little, M. H. Sulfanilamide and Related Compounds in Experimental Tuberculosis, *Proc Soc Exper Biol &*

a recent report, sulfanilamide inhibited tuberculosis in guinea pigs, but large doses were needed. No effect was noted in rabbits inoculated intravenously with bovine tubercle bacilli. The drug had little effect on the course of Friedlander bacillus infections in mice⁴² or on that of canine filariasis⁴³. A few patients with trachoma were apparently aided by sulfanilamide⁴⁴. No effect was noted on tertian malaria,⁴⁵ which is disappointing in the face of rather optimistic reports made by others in the previous year. In monkeys experimentally infected with *Plasmodium knowlesi* Coggeshall⁴⁶ observed favorable effects from sulfanilamide, employed both prophylactically and therapeutically. The drug was without effect on infections caused by avian plasmodia.

Thompson and Greenfield⁴⁷ studied 1,219 patients with measles and 244 with whooping cough. The patients to whom sulfanilamide was given presented fewer complications, such as otitis media, pneumonia and catarrh. The drug was ineffective in measles⁴⁸. In 4

Med **40** 418-420 (March) 1939. Ballou, H. C., and Guernon, A. Effect of Sulfanilamide on the Development of Experimental Tuberculosis in the Guinea Pig, *J Thoracic Surg* **8** 188-194 (Dec) 1938. Buttle, G. A. H., and Parrish, H. J. Treatment of Tuberculosis in Guinea Pigs with Sulphanilamide, *Brit M J* **2** 776-777 (Oct 15) 1938. Kolmer, J. A., Raiziss, G. W., and Rule, A. Sulfanilamide and Derivatives in the Treatment of Experimental Tuberculosis of Guinea Pigs, *Proc Soc Exper Biol & Med* **39** 581-584 (Dec) 1938. Greey, P. H., Campbell, H. H., and Culley, A. W. Effect of Sulfanilamide on Experimental Tuberculosis in the Guinea Pig, *ibid* **39** 22-24 (Oct) 1938. Dietrich, H. F. Prontosil in Experimental Tuberculosis, *Am Rev Tuberc* **38** 388-392 (Sept) 1938.

42 Gross, P., Cooper, F. B., and Lewis, M. Sulfanilamide Therapy of Friedlander-Bacillus Infections of Mice, *Proc Soc Exper Biol & Med* **39** 12-13 (Oct) 1938.

43 Brown, H. W. Ineffectiveness of Sulfanilamide in the Treatment of Canine Filariasis, *Proc Soc Exper Biol & Med* **39** 98-100 (Oct) 1938.

44 Lian, B. Sulfanilamide in the Treatment of Trachoma, *Geneesk tijdschr v Nederl-Indie* **78** 1058-1065 (May 3) 1938. Loe, F. Sulfanilamide Treatment of Trachoma, *J A M A* **111** 1371-1372 (Oct 8) 1938.

45 Hall, W. E. B. Sulfanilamide in Tertian Malaria, *J Pharmacol & Exper Therap* **63** 353-368 (Aug) 1938. Faget, G. H., Palmer, M. R., and Sherwood, R. O. Unsuccessful Treatment of Malaria with Sulfonamide Compounds, *Pub Health Rep* **53** 1364-1366 (Aug 5) 1938.

46 Coggeshall, L. T. Prophylactic and Therapeutic Effect of Sulfonamide Compounds in Experimental Malaria, *Proc Soc Exper Biol & Med* **38** 768-773 (June) 1938. Cure of *Plasmodium knowlesi* Malaria in Rhesus Monkeys with Sulfanilamide and Their Susceptibility to Reinfection, *Am J Trop Med* **18** 715-722 (Nov) 1938.

47 Thompson, A. R., and Greenfield, C. R. M. Chemotherapy in Measles and Whooping Cough. Prophylaxis and Treatment of Complications, *Lancet* **2** 991-993 (Oct 29) 1938.

48 Anderson, T. Sulfanilamide in the Treatment of Measles, *Brit M J* **1** 716-718 (April 8) 1939.

patients sulfanilamide seemed to diminish the severity of the eruption as compared with that in 3 untreated patients

Two patients with actinomycosis improved after treatment with sulfanilamide,⁴⁹ but the drug had no effect in a case of rabies in man⁵⁰ nor did it change the course of experimental rabies⁵¹ Experimental plague in rodents was cured with sulfapyridine, but antiplague serum was equally effective⁵² Sulfanilamide was slightly more effective than sulfapyridine in prolonging the life of mice experimentally infected with *Bacillus typhosus*⁵³

Of 7 patients with smallpox who were treated with sulfanilamide, 4 showed only an evanescent macular eruption as compared with 3 untreated ones, in whom the typical eruption appeared⁵⁴

PNEUMONIA

Pneumococcic Pneumonia—A number of studies were made to throw more light on the pathogenesis of pneumococcic pneumonia and on that state known as "diminished resistance," which presumably accounts for the invasion of pathogenic micro-organisms and the development of pneumonia Robertson⁵⁵ summarizes his previous contributions and concludes that pneumococci implanted in the terminal air sacs are dispersed throughout the lobe principally by the edema fluid which spreads to adjacent air passages and through the alveolar pores He modified his former conclusions as to the importance of macrophages in the process of recovery and now believes that macrophages play only a part in recovery The cellular reaction may be secondary to some more fundamental change affecting the pneumococci so that they can be disposed of Recovery from pneumonia, he believes, is due to two factors, one which localizes the infection and the other a local process involving macrophages which enables the body to rid itself

49 Miller, E M, and Fell, E H Sulfanilamide Therapy in Actinomycosis, *J A M A* **112** 731 (Feb 25) 1939 Hall, W E B Sulfanilamide and Actinomycosis, *ibid* **112** 2190 (May 27) 1939

50 Hart, B F, and Evans, E Ineffectiveness of Sulfanilamide in Rabies from Vaccinated Dogs, *J A M A* **112** 731-732 (Feb 25) 1939

51 Gross, P, Cooper, F B, and Lewis, M Chemotherapy of Experimental Rabies of Rats, *Proc Soc Exper Biol & Med* **40** 649-650 (April) 1939

52 Schutze, H Chemotherapy in Plague Infections, *Lancet* **1** 266-268 (Feb 4) 1939

53 Kolmer, J A, and Rule, A M Sulfanilamide and Sulfapyridine in Treatment of Experimental B Typhosus (*Eberthella Typhosus*) Infection of Mice, *Proc Soc Exper Biol & Med* **40** 615-619 (April) 1939

54 McCammon, W D Sulfanilamide in the Treatment of Smallpox, *J A M A* **112** 1936-1937 (May 13) 1939

55 Robertson, O H Recent Studies on Experimental Lobar Pneumonia Pathogenesis, Recovery and Immunity, *J A M A* **111** 1432-1437 (Oct 15) 1938

of pneumococci. If both processes are active, recovery ensues, if either one or both fail, death follows. After recovery from experimental pneumonia, a high degree of local immunity persists in the lobe involved as long as macrophages are present in the alveoli. Others^{55a} found that in infected guinea pigs at the same general period the mononuclear cells increase in number regardless of the outcome.

Nungester and Klepser⁵⁶ made experiments with a view to determining what constitutes "lowered resistance." Exposure to cold, deep anesthesia and intoxication with alcohol, respectively, favored aspiration of bacteria-laden mucus placed in the nose. These factors have long been known to favor the onset of pneumonia, and recently more evidence has been added to demonstrate the effect of chilling the body, which causes peripheral vasoconstriction, stasis, anoxemia and impairment of the function of phagocytes in the nasal mucosa.⁵⁷ Further studies⁵⁸ on the subject tend to show how intoxication with alcohol reduces the resistance to pneumococcal infections. Alcohol apparently has no direct effect on the power of phagocytes to engulf pneumococci but appears to exert some action on capillary walls which prevents egress of leukocytes into the surrounding tissue. Whether the effect is caused by depression of the normal function locally or by disturbance of the central nervous system is uncertain, but the mechanism involved is doubtless one of great importance.

French investigators⁵⁹ studied the action of the lungs on bacteria in the blood. Perfused lungs were found to be an effective filter for bacteria added to the blood with which the tests were made.

Frisch⁶⁰ watched the behavior of phagocytes and pneumococci in the sputum of patients treated with specific immune serum and with sulfanilamide. Usually clumping of capsulated pneumococci and increased phagocytosis appeared shortly after serum treatment, but

55a Fleischer, M. S., and Rich, G. T. Mononuclear Leukocytes in Blood of Guinea Pigs Experimentally Infected with *Pneumococcus*, *Proc Soc Exper Biol & Med* **41** 7-10 (May) 1939.

56 Nungester, W. J., and Klepser, R. G. A Possible Mechanism of Lowered Resistance to Pneumonia, *J Infect Dis* **63** 94-102 (July-Aug) 1938.

57 Taylor, H. M., and Dyrenforth, L. Y. Chilling of the Body Surfaces: Its Relationship to Aural and Sinus Infections, *J A M A* **111** 1744-1746 (Nov 5) 1938.

58 Pickrell, K. L. The Effect of Alcoholic Intoxication and Ether Anesthesia on Resistance to Pneumococcal Infection, *Bull Johns Hopkins Hosp* **63** 238-245 (Oct) 1938.

59 Binet, L., and Jaulmes, C. Lungs and Microbes, *Presse med* **46** 1281-1282 (Aug 24) 1938.

60 Frisch, A. W. Sputum Studies in Lobar Pneumonia. Phagocytosis and the Effect of Serum Therapy, *Proc Soc Exper Biol & Med* **39** 473-477 (Dec) 1938, Encapsulated Pneumococci in Sputum for Control of Serum Therapy, *ibid* **40** 495-496 (March) 1939.

similar changes were often noted in untreated patients. According to Frisch, the test may be used as a method to control serum therapy.

Numerous papers⁶¹ were published during the year on the treatment of pneumonia caused by pneumococci of various types with refined horse serum or rabbit serum. All record favorable results, with the death rate reduced to from 33 to 7 per cent. Horn^{61,1} observed the effects of serum therapy in 120 patients and reports the death rate reduced to 33 per cent, a figure lower than that reported with sulfapyridine therapy. Rabbit serum caused chills in 65 per cent of Loughlin's^{61a} 69 patients, but the incidence of serum disease was lower than that following the use of horse serum.

It is often stated that pneumococcic lobar pneumonia in northern Europe is a relatively benign disease as compared with that in the United States. According to Nissen,^{61g} however, the mortality rate in Denmark is between 25 and 40 per cent. By giving specific immune serum within the first four days of illness he reduced the death rate to 10 per cent.

Chemotherapy with sulfanilamide and sulfapyridine is discussed on pages 364 to 366. MacLachlan and his associates⁶² report beneficial effects

61 (a) Loughlin, E. H., Bennett, R. H., and Spitz, S. H. The Treatment of Lobar Pneumonia with Rabbit Antipneumococcus Serum, *J. A. M. A.* **111** 497-502 (Aug. 6) 1938. (b) Baastrup, S., Transbøl, K., and Nielsen, O. P. Experiences with Serum Treatment of Lobar Pneumococcic Pneumonias, *Ugeskr. f. læger* **100** 1195-1201 (Oct. 27) 1938. (c) Blankenhorn, M. A. The Present Status of the Serum Therapy of Lobar Pneumonia, *J. A. M. A.* **111** 1260-1262 (Oct. 1) 1938. (d) Nemir, R. L. Serum Treatment of Pneumonia in Childhood, *J. Pediat.* **13** 219-235 (Aug.) 1938. (e) Plummer, N. The Use of Serum in the Treatment of the Higher Types of Pneumonia, *J. A. M. A.* **111** 694-698 (Aug. 20) 1938. (f) Andersen, W. T. Experiences with Serum Treatment of Croupous Pneumonia, *Ugeskr. f. læger* **100** 966-968 (Aug. 25) 1938. (g) Nissen, N. I. Serotherapeutic Studies on Lobar Pneumonia, Especially Treatment with Rabbit Antipneumococcus Serum, *Acta med. Scandinav.* **98** 231-261, 1939. (h) Finland, M., and Brown, J. W. Specific Treatment of Pneumococcus Type I Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, *Am. J. M. Sc.* **197** 141-280 (Feb.) 1939. (i) Brown, J. W., and Finland, M. Specific Treatment of Pneumococcus Type II Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, *ibid.* **197** 369-380 (March) 1939. (j) Finland, M., and Brown, J. W. Specific Treatment of Pneumococcus Type V and Type VII Pneumonias, *ibid.* **197** 381-390 (March) 1939. (k) Treatment of Pneumococcus Type III Pneumonia with Specific Serum and Sulfanilamide, *New England J. Med.* **220** 365-372 (March 2) 1939. (l) Horn, B. Pneumococcic Lobar Pneumonia. Report of Two Hundred and Forty-Five Cases with Special Reference to Specific Serum Therapy, *Ann. Int. Med.* **12** 922-931 (Jan.) 1939. (m) Rogers, E. S., and Gooch, M. E. Type I Pneumococcus Pneumonia. Observations from Study of Two Thousand Cases Treated with Specific Serum, *New York State J. Med.* **38** 1369 (Nov. 1) 1938.

62 MacLachlan, W. W. G., Johnston, J. M., Bracken, M. M., and Crum, G. E. Treatment of Pneumococcic Pneumonia by Hydroxyethylapocupreine, *Am. J. M. Sc.* **197** 31-39 (Jan.) 1939.

from the treatment of pneumococcic pneumonia with hydroxyethylapocupreine dihydrochloride. The study of Rogers and Gooch^{61m} emphasizes the danger of pregnancy as a factor predisposing to pneumonia. The pregnancy rate for patients with type I pneumonia was 6.6 per cent, compared with an estimated rate of 2.2 per cent in a similar age group in the female population. The last four months of pregnancy is the most dangerous time. The same authors show that nonspecific serum has no effect on the course of pneumonia.

Finland and Dublin⁶³ report studies of 212 cases in which pneumococcic pneumonia complicated pregnancy and the puerperium. About 1 of every 8 women of child-bearing age who had pneumonia were pregnant, 0.63 per cent of all women admitted during pregnancy or parturition had pneumonia, and in 1.2 per cent of women of this age with pneumonia the condition was complicated by pregnancy. Pneumonia accounts for 1 death in every 5,000 deliveries and causes about one half of the maternal deaths from nonobstetric factors. The pneumonia of pregnant women is less often typical as compared with that of nonpregnant women of this age, although the distribution of pneumococcic types among the pregnant women is about the same as among the nonpregnant. Bacteremia was more frequent in pregnant women, and the death rate from pneumonia among them was higher. The death rate from pneumonia was high (45 to 50 per cent) among those who contracted the disease after the sixth month of pregnancy, among those whose pregnancy was terminated during the course of the disease and among those who were not treated with serum. Among 79 patients delivered during pneumonia there were 35 (44 per cent) whose infants were stillborn and 13 whose babies died soon after birth. Labor was often succeeded by shock. All abortions occurred before the seventh month of pregnancy, and none of the babies survived. Of 54 mothers who had pneumonia after delivery at term, 46 had normal babies.

Cecil⁶⁴ made an interesting study of the nature of pneumonia encountered in private practice. From time to time one hears that patients with pneumonia can be treated best at home and that the mortality rate in the ones treated at home is lower than in the ones treated in hospitals⁶⁵. This may be true for pneumonia in general but when one compares the different types of pneumonia caused by pneumococci of specific types there is little difference in mortality whether the patients are kept at home or not. A great many statements made concerning

63 Finland, M., and Dublin, T. D. Pneumococcic Pneumonias Complicating Pregnancy and the Puerperium, *J. A. M. A.* **112** 1027-1032 (March 18) 1939.

64 Cecil, R. L., and Lawrence, E. A. Pneumonia in Private Practice. A Study of Nine Hundred and Eleven Cases, *J. A. M. A.* **111** 1889-1894 (Nov. 19) 1938.

65 Cooper, E. R., and Cecil, R. L. Pneumonia in Private Practice, Correspondence, *J. A. M. A.* **112** 168-169 (Jan. 14) 1939.

the supposed mildness of pneumonia in general practice, particularly in country districts, are inaccurate. Unless etiologic diagnoses are made with bacteriologic methods, accurate conclusions cannot be reached.

Hirsch⁶⁶ found the average cost of the treatment of a patient with pneumonia to be \$167.60. In three quarters of the cases the cost is over \$80. The average cost of serum for a patient in a hospital ward is \$59. The two major items of expense are hospitalization and the physician's services.

Significance of Pneumococci of the Higher-Numbered Types—I believe that caution should be used in arriving at an etiologic diagnosis of pneumonia in a patient in whose sputum pneumococci of one of the higher-numbered types are found. Whenever pneumococci of types I, II, III, V, VII, VIII or XIV are present in the sputum of a patient whose illness commenced suddenly with a chill and other signs and symptoms characteristic of lobar pneumonia, one can be almost certain that they are of etiologic significance. But it is often doubtful that pneumococci of any other type are of primary etiologic importance when found in the sputum of a patient with patchy atypical pneumonia, a low leukocyte count and other uncharacteristic signs. Many other bacteria and viruses may cause mild or severe forms of pneumonia, and the pneumococci found in the sputum may be mere saprophytes, which are habitually found in the nasopharyngeal secretions of the patient. If pneumococci are found in the blood stream, they are most likely the cause of the disease, and in many mild infections of the lung pneumococci may, of course, be serious secondary invaders. The decision in many cases is a difficult one to make.

An unusual complication of pneumonia, namely, acute hemorrhagic ulcerative gastroenteritis, was reported under the name of Dieulafoy's disease⁶⁷. It is hardly justifiable to call the condition described by the authors pneumococcic gastroenteritis, since their data do not show that the pneumococcus was the cause of the complication.

Prophylaxis—Studies on the experimental vaccination of members of the Civilian Conservation Corps have progressed to such a degree that certain facts may now be stated⁶⁸. A soluble pneumococcic

66 Hirsch, J. A Study of the Economics of Pneumonia. The Costs of Diagnosis and Treatment of Six Hundred and Twenty-Five Cases in New York City, Pub Health Rep **53** 2153-2168 (Dec 9) 1938.

67 Sanford, C. H., Hughes, J. D., and Weems, J. Pneumonia Complicated by Acute Pneumococcic Hemorrhagic Ulcerative Gastroenteritis (Dieulafoy's Disease), Arch Int Med **62** 597-603 (Oct) 1938.

68 Felton, L. D. Studies on Immunizing Substances in Pneumococci VII. Response in Human Beings to Antigenic Pneumococcus Polysaccharides, Types I and II, Pub Health Rep **53** 1855-1877 (Oct 21) 1938. Ekwurzel, G. M., Simmons, J. S., Dublin, L. I., and Felton, L. D. VIII. Report on Field Tests to Determine the Prophylactic Value of a Pneumococcus Antigen, *ibid* **53** 1877-1893 (Oct 21) 1938.

polysaccharide antigen prepared by Felton was used as an immunizing agent against pneumococci of types I and II. The results are given in the accompanying table.

Although the results are not particularly striking, since no serious outbreaks of pneumonia have occurred there is some indication that the antigen may be effective as an immunizing agent. There is evidence also that the antigen is more effective in adolescents than in persons of more advanced age. The antigen did not lower the incidence of other infections of the respiratory tract. Further studies are under way.

Walsh and Cannon⁶⁹ found that nasal instillation of small numbers of pneumococci of type I in rabbits led to fatal septicemia in 70 per cent of them unless they had been vaccinated by dropping killed or autolyzed cultures of type I pneumococci into the nares. Other forms of vaccination, specific or unspecific, were of no value. Since the animals vaccinated intranasally did not have specific antibodies in the

Results of Experimental Immunization with Pneumococcus Types I and II in Civilian Conservation Corps

Vaccinated Group			Control Group		
Persons Studied	Cases of Pneumonia	Deaths	Persons Studied	Cases of Pneumonia	Deaths
3,126	0	0	9,000	8	0
7,500	13	0	7,500	23	2
15,000	18	0	18,000	39	0

blood stream, it seems that the immunity induced was local, involving only the mucous membrane.

Smillie⁷⁰ believes the prevention of colds and of overcrowding more important in the control of pneumonia than isolation or quarantine of patients with pneumonia or of those in contact with them. It seems to me, however, that since most persons in contact with pneumococcal pneumonia become temporary carriers of the pneumococcus causing the disease, isolation would at least reduce the number of carriers. This view is shared by Cincinnati internists⁷¹ and by others who previously cited numerous examples of pneumonia apparently contracted by contact with a patient suffering from pneumonia. Colds, they believe, are

⁶⁹ Walsh, T. E., and Cannon, P. R. Immunization of the Respiratory Tract. Comparative Study of Antibody Content of Respiratory and Other Tissues Following Active, Passive and Regional Immunization, *J. Immunol.* **35** 31-46 (July) 1938.

⁷⁰ Smillie, W. G. The Prevention of Pneumonia, *New York State J. Med.* **38** 1485-1489, 1938.

⁷¹ Benjamin, J. E., Ruegsegger, J. M., and Senior, F. A. Cross Infection in Pneumococcal Pneumonia, *J. A. M. A.* **112** 1127-1130 (March 25) 1939.

important in predisposing to pneumonia of the homologous type. They urge segregation of patients with colds by the methods employed in wards for patients with contagious diseases.

Other Forms of Pneumonia—Hadfield⁷² makes a further report on the so-called rheumatic pneumonia. While he agrees in general with those who have given previous descriptions, he feels that the sequence of changes has not been given clearly. There is first widespread fibrinous alveolitis, which is followed by infiltration of mononuclear cells. True Aschoff nodes are difficult to identify in lung tissue.

Cramer⁷³ describes a form of pneumonia caused by inhalation of nitric oxide compound gas. It is characterized by military bronchopneumonia.

Chown⁷⁴ suggests that the metaplastic reaction in the alveoli and bronchioles in the so-called giant cell pneumonia of infants described by Hecht, Karsner and others may be the result of deficiency of vitamin A.

Dickson⁷⁵ publishes more evidence to show that coccidioidomycosis commences as a primary infection of the lungs. In most cases the infection is mild, and recovery is the rule. The disease is usually mistaken for a simple cold or for influenza. Erythema nodosum commonly occurs, even in mild forms. In a few cases the primary attack subsides to be followed later by generalization of the process as a pyemic infection which is highly fatal.

Little attention has been given by Americans to the syndrome called transient hyperergic infiltration of the lung with eosinophilia, described by Löffler in 1931. It may be identical with a peculiar form of "allergic" pneumonia recognized since 1912. Since 1931 numerous Europeans have published reports of cases.⁷⁶ The disease is perhaps seldom recognized, because of its mildness. The onset is sudden, with rapidly forming diffuse shadows in the lung, which disappear after three to eight days. Fever is seldom noted, but there may be cough with or without pleural

72 Hadfield, G. The Rheumatic Lung, *Lancet* **2** 710-711 (Sept 24) 1938.

73 Cramer, G. Pneumonia Caused by Gaseous Nitric Oxide Compounds, *Arch f Gewerbepath u Gewerbehyg* **9** 1-12 (Nov 12) 1938.

74 Chown, B. Giant Cell Pneumonia of Infancy as a Manifestation of Vitamin A Deficiency, *Am J Dis Child* **57** 489-505 (March) 1939.

75 Dickson, E. C., and Gifford, M. A. Coccidioides Infection (Coccidioidomycosis). II. The Primary Type of Infection, *Arch Int Med* **62** 853-871 (Nov) 1938.

76 Gravesen, P. B. Transitory Lung Infiltrations with Eosinophilia, *Acta med Scandinav* **96** 523-534, 1938. Leitner, L. J. Hyperergische, fluchtige, mit Eosinophilie eingehende Infiltrate der Lungen bei Tuberkulose und Abortipneumonien, *ibid* **97** 473-507, 1938. Ramsay, H., and Scadding, J. G. Benign Bronchopulmonary Inflammations Associated with Transient Radiographic Shadows, *Quart J Med* **32** 79-95 (April) 1939.

pain, and the sputum may be frothy. The cause is unknown, but the condition is thought to be hypereirgic in nature, involving the interstitial tissue and the alveoli rather than the bronchi, as in asthma.

A "NEW" INFECTION OF THE RESPIRATORY TRACT

During 1938 a number of cases of a peculiar form of pneumonia in Philadelphia came to my attention.⁷⁷ Similar cases were noted in New York, Albany, Boston, Washington, D. C., the state of Georgia, St. Louis, Minneapolis,⁷⁸ Chicago, the state of Oregon⁷⁹ and England.⁸⁰

The infection started suddenly or gradually, and in the early stage was often regarded as a cold or influenza. There was occasionally a brief period of remission before the temperature rose to high levels. The inflammation spread from the nose or throat to the bronchi, bronchioles and lungs, where a diffuse atypical pneumonia finally developed. The disease was characterized by hoarseness, dyspnea, cyanosis, sweating, stupor, cough with a minimal amount of sputum, high fever and relative bradycardia. In 2 patients signs and symptoms of encephalitis developed. One patient died. The leukocyte count was normal or slightly increased. In a few patients the clinical condition at the height of the illness strongly resembled typhoid fever or psittacosis.

In an attempt to find the cause of the disease Stokes, Kenney and Shaw⁸¹ and Francis and Magill obtained nasopharyngeal washings from most of my patients and inoculated ferrets. From the nasal washings of one patient and from the blood serum of another a filtrable agent was recovered, which caused bacteria-free mononuclear cell pneumonia and encephalitis in ferrets and white mice.

Unfortunately, the virulence of the virus was not maintained in animals, and the virus was lost after ten to fifteen passages, before specific protection tests and other tests could be made to verify its etiologic significance. The virus was either (a) the cause of the disease described, (b) a commensal or (c) a virus found in rodents. The last possibility is not very great, since the virus was found by different investigators in different cities, it was different from other known

77 Reimann, H. A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filtrable Virus, *J. A. M. A.* **111** 2377-2384 (Dec. 24) 1938.

78 McKinlay, C. A. Acute Diffuse Bronchiolitis, *Journal-Lancet* **59** 90-91 (March) 1939.

79 Miller, F. N., and Hayes, M. G. Bronchopneumonia of Mild Severity at the University of Oregon, *Northwest Med.* **38** 12-14 (Jan.) 1939.

80 Andrewes, C. H. Epidemic Influenza, *Lancet* **1** 589-591 (March 11) 1939.

81 Stokes, J., Kenney, A. S., and Shaw, D. R. A New Filtrable Agent Associated with Respiratory Infections, *Tr. Coll. Physicians Philadelphia* **6** 329-333 (Feb.) 1939.

viruses, it died out during passage (if of animal origin it probably would have persisted), and it was obtained from the nasal washings and blood of 2 members of the same family

The question arose whether the infection is a "new" disease or whether it is a member of a group of atypical infections heretofore called colds, bronchopneumonia or capillary bronchiolitis. I regarded it rather as a newly recognized severe form of an otherwise mild and perhaps commonly encountered infection of the respiratory tract. The infection as described has many features in common with pneumonia caused by other filtrable viruses, such as the pneumonia of psittacosis, vaccinia, measles or influenza. One wonders whether the epidemic disease in the Faroe Islands described by Rasmussen⁸² as a psittacosis-like disease is not the same as that described here. Stahel⁸³ studied an explosive outbreak of an infectious disease in a Swiss regiment. Of 930 soldiers, 108 had catarrhal symptoms with profuse perspiration, myalgia and diphasic fever. Because 6 of the affected soldiers had persistent headache, stiffness of the neck and myalgia, Stahel regarded the epidemic as one of poliomyelitis in spite of a morbidity rate of 14 per cent and no sequels. From the brief description given it seems more likely that it was predominantly an infection of the respiratory tract which involved the central nervous system in a few cases.

A virus obtained from other patients with infection of the respiratory tract which caused meningitis and pneumonitis in animals was studied by Francis and Magill⁸⁴.

In view of the fact that experimental animals, especially white mice, guinea pigs and rabbits, harbor numerous native viruses that are filtrable, it is necessary to use caution in interpreting a disease observed to occur in such animals after injection of materials obtained from human patients, as signifying the transfer of disease from these patients. Gordon, Freeman and Clampitt⁸⁵ reported the discovery in mice of a filtrable agent which causes pneumonia. The disease is easily confused with that caused by the inoculation of mice with the virus of epidemic influenza except for the absence of metaplastic replacement of the bronchiolar epithelium. Further differentiating it from influenza is a focal necrosis

82 Rasmussen, R. L. Er primer epidemisk alveolopneumoni og psittacosis samme sygdoms? *Ugeskr. f. læger* **100** 989-998 (Sept 1) 1938

83 Stahel, H. Die Poliomyelitis Epidemie, Schweiz. med. Wchnschr. **68** 86-91, 1938. Epidemic of Poliomyelitis in a Regiment, *Foreign Letters*, J. A. M. A. **111** 74 (July 2) 1938.

84 Francis, T., and Magill, T. P. An Unidentified Virus Producing Meningitis and Pneumonitis in Experimental Animals, *J. Exper. Med.* **68** 147-160 (Aug.) 1938.

85 Gordon, F. B., Freeman, G., and Clampitt, J. M. A Pneumonia-Producing Filtrable Agent from Stock Mice, *Proc. Soc. Exper. Biol. & Med.* **39** 450-451 (Dec.) 1938.

of the live¹ which occurs. Horsfall and Hahn⁸⁶ likewise report a virus from normal mice capable of inciting pneumonitis when inoculated intranasally into normal mice. Their virus, however, was not the same as that described by the aforementioned observers or as mine, it was strictly pneumonotropic in mice, it was nonpathogenic when inoculated intraperitoneally or intracerebrally, and it was not virulent for ferrets.

At the May meeting of the Association of American Physicians Stokes and I gave further evidence to support the view that the disease I described in 1938 was the severe form of a widely distributed infection of the respiratory tract. In February and March of 1939 a widespread epidemic broke out in Philadelphia. Nearly 50 per cent of a group of 800 persons comprised of nurses, students and interns at Jefferson Hospital were ill during this time. Of this group, 78 per cent were mildly ill and ambulatory, 15 per cent were moderately ill and confined to bed, and 7 per cent had the severe form of the disease, with pneumonia. None died. No definite evidence of the isolation of a virus was found when nasopharyngeal washings were inoculated into ferrets by Stokes and Shaw. The virus of epidemic influenza, or evidence of its presence, was not obtained.

A similar epidemic was noted in Ithaca, N. Y., among university students. The observers⁸⁷ preferred to call the disease acute interstitial pneumonitis, but no necropsy material was available to support this description. I had previously mentioned the term "virus pneumonia," but this term also is not desirable unless a virus can be proved to cause the disease. Furthermore, in only a small percentage of those ill were the lungs involved. Since an etiologic diagnosis is preferable to an anatomic one, it is best not to give the entity a definite name until its cause can be found. It is perhaps better, also, to regard it as a newly described disease rather than a new disease.

Goodpasture and his co-workers⁸⁸ observed a hitherto undescribed "virus pneumonia" in 5 infants. The virus invasion appeared to be secondary to measles and whooping cough and seemed to pave the way for bacterial invasion of the lung. Animals could not be infected by experimental inoculation of lung tissue. The virus was not that of herpes simplex nor that of the so-called inclusion disease of infants. The pulmonary lesions showed characteristic intranuclear inclusions, present almost exclusively in the epithelial cells of the trachea, bronchi

86 Horsfall, F. L., and Hahn, R. G. A Pneumonia Virus of Swiss Mice, *Proc Soc Exper Biol & Med* **40** 684-686 (April) 1939.

87 Smiley, D. F., Showacre, E. C., Lee, W. F., and Ferris, H. W. Acute Interstitial Pneumonitis. A New Disease Entity, *J A M A* **112** 1901-1904 (May 13) 1939.

88 Goodpasture, E. W., Auerbach, S. H., Swanson, H. S., and Cotter, E. F. Virus Pneumonia of Infants Secondary to Epidemic Infections, *Am J Dis Child* **57** 997-1011 (May) 1939.

and alveoli. Epithelial necrosis and ulceration of the tracheal and bronchial mucosa and interstitial pneumonia followed.

INFLUENZA

According to Francis and Magill,⁸⁹ there were marked differences and striking similarities in antigenic characteristics among 24 strains of the virus of epidemic influenza. A rough grouping of strains is possible, but the characteristics of one group merge with those of another. The differences which were found, they believe, scarcely warrant the designation of types. The conclusions of Smith and Andrewes⁹⁰ on the same subject, published in the same journal, differ somewhat from those of Francis and Magill. To account for the divergent results, the English investigators suggest that the strains studied by Francis and Magill all fall into a group which in England is regarded as "intermediate." Smith and Andrewes classify strains of influenza virus into three main categories, namely, highly specific, relatively nonspecific and intermediate strains. It is obvious that many strains do exist, which is a consideration of importance for epidemiologic and prophylactic reasons. This multiplicity may account for second attacks, the latter being due to strains antigenically dissimilar to those causing the first attack. It is still unknown whether the various types of strains are of stable antigenic constitution or whether significant variation occurs. Several apparently different strains may be encountered in a single epidemic.

Francis and Stuart-Harris⁹¹ made studies similar to those reported by Straub in 1937 and found the virus of influenza to cause a specific injury of the nasal mucosa in ferrets. Study of the process of repair showed on about the sixth or eighth day an abnormal type of epithelium that was resistant to further virus infection and to injury by zinc sulfate. After twenty-one days the membrane was again normal in type and susceptible to injury. The destruction of the membrane in the early period seems to permit invasion by pathogenic bacteria. Stuart-Harris⁹² caused a strain of influenza virus to become neurotropic in young mice.

89 Magill, T. P., and Francis, T. Antigenic Differences in Strains of Epidemic Influenza Virus, *Brit J Exper Path* **19** 273-284 (Oct) 1938. Francis, T. and Magill, T. P. Cross-Immunization Tests in Mice, *ibid* **19** 284-292 (Oct) 1938.

90 Smith, W., and Andrewes, C. H. Serologic Races of Influenza Virus, *Brit J Exper Path* **19** 293-314 (Oct) 1938.

91 Francis, T., and Stuart-Harris, C. H. Studies on the Nasal Histology of Epidemic Influenza Virus in the Ferret, *J Exper Med* **68** 813-830 (Dec) 1938.

92 Stuart-Harris, C. H. A Neurotropic Strain of Human Influenza Virus, *Lancet* **1** 497-499 (March 4) 1939.

by passage on chorio-allantoic membrane Leish⁹³ calls attention to the remarkable tissue specificity of influenza virus In tissue culture experiments the virus grew best in lungs of embryos The more embryonic the tissue, however, the wider the range of organs in which growth was possible

At the meeting of the American College of Physicians in the spring of 1938 Goodpasture reported the culture of influenza virus in chick embryos Vaccine made from such cultures may eventually prove practical for the prevention of influenza

Shope⁹⁴ suggests that lungworm larvae from pigs which harbor influenza virus may carry the virus to earthworms, which in turn are eaten by other pigs, which may then acquire the infection in a subclinical form Influenza may be provoked in these hogs by injecting *Haemophilus influenzae suis* intramuscularly or by nonspecific measures, such as injecting calcium chloride solution intrapleurally

Magill and Francis⁹⁵ demonstrated a flocculation reaction when serums of patients convalescent from influenza were mixed with suspensions of lung tissue from mice infected with influenza virus It was not definitely established whether the reaction was specific for the virus of influenza or not

ANIMALS AS HOSTS OF INFECTIOUS AGENTS OF MAN

The importance of animals as reservoirs of infections which may spread to man is receiving an increasing amount of attention Although a few of the more obvious infections which involve both man and animals have long been known, such as glanders, anthrax, foot and mouth disease, rabies, plague, tuberculosis and smallpox, other infections, less striking in their manifestations or in their mortality rate, have been dealt with only in recent years They include tularemia, undulant fever, the typhus-spotted fever group of rickettsial diseases, those caused by filtrable viruses, such as choriomeningitis, "equine" encephalomyelitis, jungle yellow fever, influenza, swineherd's disease, psittacosis and louping ill, and the spirochetal group with rat-bite fever, relapsing fever and Weil's disease

To emphasize the importance of this group of diseases involving both man and animals I have gathered together the following information as indicative of the advances in knowledge made in this direction in 1938

93 Tissue Specificity of Influenza Virus, Foreign Letters, J A M A **112** 1615 (April 22) 1939

94 Shope, R E An Intermediate Host for the Swine Influenza Virus, Science **89** 441-442 (May 12) 1939

95 Magill, T P, and Francis, T A Flocculation Phenomenon with Human Sera and Suspensions of the Virus of Epidemic Influenza, Proc Soc Exper Biol & Med **39** 81-84 (Oct) 1938

Lymphocytic Choriomeningitis—Armstrong and Sweet⁹⁶ report 2 cases of lymphocytic choriomeningitis from Washington, D C Gray house mice trapped in the homes of the patients were found to harbor the virus which causes the disease The virus was not present in mice caught elsewhere Mice were, therefore, incriminated as a reservoir of the disease from which man is infected It seems to me, however, that, as in the controversy on human influenza and hog influenza, it is not possible to tell whether the mice did not contract the infection from the human patients

Coggeshall⁹⁷ proved experimentally that mosquitoes may transmit the virus of lymphocytic choriomeningitis from infected monkeys or guinea pigs to normal ones Mosquitoes are infectious as early as the fourth day and as late as the fifteenth day after feeding on a sick animal

Howard⁹⁸ points out how important it is to make an etiologic diagnosis in cases of this disease, since, she believes, other agents may give rise to similar signs and symptoms

Encephalomyelitis—In 1931 Meyer, Haring and Howitt reported the discovery of a virus which caused an outbreak of encephalomyelitis among horses and mules in California Because of the occurrence of the disease in these animals it was called equine encephalomyelitis Later Meyer suggested that human beings may contract the disease from horses and reported 3 cases in which this may have occurred In 1936 an epidemic among horses in Montana was recognized⁹⁹

In 1935 the disease was noted among horses in the eastern part of the United States, but the virus isolated differed somewhat serologically from that causing the western variety of this disease The discovery of the disease in different parts of the country brings up the question raised before concerning tularemia, undulant fever and the eastern variety of Rocky Mountain spotted fever—i e, whether it is a new disease and whether it is spreading It is my belief that none of these are new diseases in the sense of never having existed before It is more likely that they appear sporadically in unrecognized form or periodically in wavelike epidemics to subside to unimportance in interepidemic periods They are diagnosed only after some one shows how to do it or after the etiologic agent is discovered

96 Armstrong, C, and Sweet, L K Lymphocytic Choriomeningitis Report of Two Cases, with Recovery of the Virus from Gray Mice (*Mus Musculus*) Trapped in the Two Infected Households, *Pub Health Rep* **54** 673-684 (April 28) 1939

97 Coggeshall, L T The Transmission of Lymphocytic Choriomeningitis by Mosquitoes, *Science* **89** 515-516 (June 2) 1939

98 Howard, M E Lymphocytic Choriomeningitis A Discussion of Its Diagnosis in Man, *J Infect Dis* **64** 66-77 (Jan-Feb) 1939

99 Cox, H R, Philip, C B, Marsh, H, and Kilpatrick, J W Observations Incident to an Outbreak of Equine Encephalomyelitis in the Bitterroot Valley of Western Montana, *J Am Vet M A* **93** 225-232 (Oct) 1938

In 1938 striking new facts were discovered concerning "equine" encephalitis. In September Fothergill and his associates¹⁰⁰ and Webster and Wright¹⁰¹ reported that they had isolated the virus of the eastern disease from human patients, fulfilling Meyer's prediction of 1933. Schoening and his associates¹⁰² then succeeded in infecting horses with the virus obtained from one of these patients. The virus caused disease when inoculated into normal horses and in those previously rendered immune to the western variety of virus but not in those immunized against the homologous eastern strain. The virus is specific and is apparently not related to the virus of lymphocytic choriomeningitis, the St. Louis type of encephalitis or von Economo's encephalitis lethargica.

In November and December several other clinical reports were published.¹⁰³ Ecklund and Blumstein^{103a} in Minnesota and Howitt^{103b} in California reported infections of the western variety in man. A detailed clinical and pathologic description of the disease as observed in 4 cases was published by a group in Boston.^{103c} It appears that an outbreak of encephalomyelitis occurred in horses in the New England states in August 1938. More than 200 horses died. At the same time encephalitis developed in numerous persons, and 30 or more were studied. The mortality rate among horses was 90 per cent. The death rate for the patients was high (25 of 38 died) in contrast with that for patients with encephalitis lethargica, but no doubt many mild attacks went unrecognized.

A surprising report came in November from Tyzzer, Sellards and Bennett,¹⁰⁴ who discovered the virus of the eastern variety of "equine"

100 Fothergill, L. D., Dingle, J. H., Farber, S., and Connerley, M. L. Human Encephalomyelitis Caused by the Virus of the Eastern Variety of Equine Encephalomyelitis, *New England J. Med.* **219** 411 (Sept. 22) 1938.

101 Webster, L. T., and Wright, F. H. Recovery of Eastern Equine Encephalomyelitis Virus from Brain Tissue of Human Cases of Encephalitis in Massachusetts, *Science* **88** 305-306 (Sept. 30) 1938.

102 Schoening, H. W., Giltner, L. T., and Shahan, M. S. Equine Encephalomyelitis Produced by Inoculation of Human Encephalitis Virus, *Science* **88** 409-410 (Oct. 28) 1938.

103 (a) Ecklund, C. M., and Blumstein, A. The Relation of Human Encephalitis to Encephalomyelitis in Horses, *J. A. M. A.* **111** 1734-1735 (Nov. 5) 1938. (b) Howitt, B. Recovery of the Virus of Equine Encephalomyelitis from the Brain of a Child, *Science* **88** 455-456 (Nov. 11) 1938. (c) Wesselhoeft, C., Smith, E. C., and Branch, C. F. Human Encephalitis. Eight Fatal Cases, with Four Due to the Virus of Equine Encephalitis, *J. A. M. A.* **111** 1735-1741 (Nov. 5) 1938. (d) Feemster, R. F. Outbreak of Encephalitis in Man Due to the Eastern Virus of Equine Encephalomyelitis, *Am. J. Pub. Health* **28** 1403-1410 (Dec.) 1938.

104 Tyzzer, E. E., Sellards, A. W., and Bennett, B. L. The Occurrence in Nature of "Equine Encephalomyelitis" in the Ring-Necked Pheasant, *Science* **88** 505-506 (Nov. 25) 1938.

encephalomyelitis in ring-necked pheasants. Numbers of these birds had been found paralyzed in Connecticut and died before shipment to the laboratory. It was suggested that the adjective "equine" might be a misnomer, the horse may simply be another species susceptible to an infection which occurs naturally in wild life. Other wild and domestic fowl are known to be susceptible to the virus, and migratory birds are implicated as a possible permanent source of infection. During the epidemic among horses in August pigeon breeders noted an unusual fatal disease among their birds. From one of the dead birds Fothergill and Dingle¹⁰⁵ isolated the virus.

The ease with which mice can be infected suggests that rodents may be a source of the disease, as they are of typhus, spotted fever, plague and tularemia. Numerous investigators have suggested that insects, particularly mosquitoes, are vectors of the infection. These problems provide experimental work for the next decade or two.

A somewhat similar disease was reported in Canada and in Venezuela. Beck and Wyckoff¹⁰⁶ studied a strain sent from South America and found it to produce a disease somewhat similar to the eastern variety of encephalomyelitis, yet immunologically it is different from both the eastern and the western variety of the virus, especially from the latter.

St. Louis Encephalitis.—In further epidemiologic studies on the outbreaks of encephalitis in St. Louis Casey and Broun¹⁰⁷ noted a concentration of cases in vicinities of sewage and refuse dumps, streams, ponds and overgrown weeds. The outbreaks had no epidemiologic features suggesting an association with bad housing, crowding or cold weather, and there were no multiple "house" cases, but every observed feature suggests a similarity to such mosquito-borne diseases as yellow fever, malaria and perhaps equine encephalitis. The outbreaks had no connection with the water supply, food supply or milk supply. They involved the same widely separated areas in two different years and occurred only in the warm months.

Armstrong¹⁰⁸ inquired into the prevalence of encephalitis in warm months. He found that the nonspecific protection resulting from the irritation of instilling cultures of nonpathogenic bacteria into the nares was sufficient to render mice resistant to subsequent intranasal inoculation with the virus of St. Louis encephalitis. Mild infections of the

105 Fothergill, L. D., and Dingle, J. H. A Fatal Disease of Pigeons Caused by the Virus of the Eastern Variety of Equine Encephalomyelitis, *Science* **88** 549-550 (Dec. 9) 1938.

106 Beck, C. E., and Wyckoff, R. W. G. Venezuelan Equine Encephalomyelitis, *Science* **88** 530 (Dec. 2) 1938.

107 Casey, A. E., and Broun, G. O. Epidemiology of Saint Louis Encephalitis, *Science* **88** 450-451 (Nov. 11) 1938.

108 Armstrong, C. Studies in the Mechanism of Experimental Intranasal Injections in Mice, *Pub. Health Rep.* **53** 2004-2012 (Nov. 11) 1938.

respiratory tract which affect so large a proportion of the population in the winter may have a similar nonspecific preventive effect during the cold months

Toxoplasmosis—Encephalitis caused by *Toxoplasma*, a protozoan parasite of various mammals and birds, has been reported in several infants recently. Wolf, Cowen and Paige¹⁰⁹ report the transmission of the infection to rabbits and mice. They suggest that human toxoplasmosis may take on clinical forms aside from encephalitis, as suggested by pathologic studies in a report from France.

De Morsier¹¹⁰ raises the question, often discussed before, of the relation of herpes simplex to encephalitis. There has been a good deal of uncertainty as to whether the two when they occur at the same time are caused by the same virus or not. This French observer believes that a relationship exists but makes no mention of attempts to prove his point with experimental studies. Similar uncertainty obtains in regard to the encephalitis of mumps,¹¹¹ that of vaccinia, postvaccinal encephalitis, postinfluenzal encephalitis and other encephalitides. Recently I noted encephalitic symptoms in 2 patients with a severe infection of the respiratory tract. A virus, presumably the cause of the disease, was isolated from one of the patients. The virus caused encephalitis and pneumonia in mice and guinea pigs. This observation strengthens the view that numerous viruses may have the capacity to affect the nervous system in addition to the tissues and organs which they usually involve.

Acute Anterior Poliomyelitis—Frauchiger and Messerli,¹¹² of Switzerland, report what they believe to be acute anterior poliomyelitis in a heifer and in hogs. The symptoms, they state, were typical of the disease in man, but no other cattle and no human beings were affected at the time. One animal was killed, and microscopic examination revealed changes in the lumbosacral portion of the spinal cord identical with those found in man. Whether the virus which caused the disease was identical with that which causes disease in man is not certain, but

109 Wolf, A., Cowen, D., and Paige, B. Human Toxoplasmosis. Occurrence in Infants as an Encephalomyelitis, Verification by Transmission to Animals, *Science* **89** 226-227 (March 10) 1939.

110 de Morsier, G. Herpetic Encephalitides. Apoplectic Form, Convulsive and Hallucinatory Form, Contagion by Herpetic Virus, *Presse med* **46** 1611 (Nov 2) 1938.

111 Fuhrmann, K. G. Nervous Complications in Epidemic Parotitis. Meningoradiculitis Basalis Parotidea, *Hospitalstid* **81** 159-168 (Feb 8) 1938. Finkelstein, H. Meningo-Encephalitis in Mumps, *J A M A* **111**.17-19 (July 2) 1938.

112 Case of Spontaneous Poliomyelitis in an Animal, *Foreign Letters*, *J A M A* **111** 74 (July 2) 1938. Frauchiger, E., and Messerli, W. Further Cases of Spontaneous Poliomyelitis in Domestic Animals (Hogs), *Schweiz med Wchnschr* **69** 74 (Jan 28) 1939.

the possibility is highly important. To test the theory further, Frauchiger and Hofmann¹¹³ inoculated 3 heifers with virus from a human patient with poliomyelitis. Each animal became ill with suggestive symptoms, and the spinal fluid gave evidence of infection. Histologic studies were not reported.

These reports led Lumsden¹¹⁴ to suggest the possibility mentioned before but never supported, namely, that the stable fly may be a carrier of the virus of this disease. The epidemiology of poliomyelitis is similar to that of other insect-borne diseases, such as typhoid fever, malaria and yellow fever.

In 1937 a sudden epidemic believed to have been poliomyelitis broke out in a Swiss regiment.⁸³ In a period of twelve days in July, 6 of 930 soldiers were taken ill with meningeal and myelitic symptoms, 16 with meningeal symptoms alone and 108 with catarrhal symptoms. There was difficulty in differentiating the disease from influenza. In reading this brief report one wonders whether this disease actually was acute anterior poliomyelitis. The morbidity rate of 14 per cent and the recovery without sequels in most of the cases do not conform with the usual description of acute anterior poliomyelitis, and no authentic cases of poliomyelitis were noted among the civil population at the same time. Furthermore, the great predominance (83 per cent) of infections of the respiratory tract, as indicated by catarrhal symptoms with profuse sweating, suggests that some pneumonotropic virus may have been operative which in an occasional patient attacked the nervous system, similar to the cases of atypical pneumonia described elsewhere in this review.

Toomey¹¹⁵ doubts whether many of the recorded cases of second attacks of poliomyelitis can be accepted as such. Other infections which follow an attack of poliomyelitis may cause further harm and aggravate the symptoms already present. Draper and Dupertius¹¹⁶ attempt to show a relationship between constitutional factors and susceptibility to poliomyelitis. Persons whose body measurements conform to a certain form seem to be more susceptible to the disease than others. In susceptible persons a tendency to overgrowth and retarded development was often noted. Particularly noticeable were a mongoloid type of eye and fetal and infant-like retardation of the eye-nose zone.

113 Frauchiger, E, and Hofmann, W. Experimental Transmission of Poliomyelitis to Cattle, *Schweiz med Wchnschr* **68** 1140-1141 (Oct 8) 1938.

114 The Stable Fly as a Possible Carrier of the Virus of Infantile Paralysis. *Science News, Science (supp)* **88** 10-11 (Oct 14) 1938.

115 Toomey, J. A. Second Attacks of Poliomyelitis, *Am J Dis Child* **59** 969-974 (Nov) 1938.

116 Draper, G, and Dupertius, C. W. The Nature of the Human Factor in Infantile Paralysis. I Peculiarities of Growth and Development, II Relation of Age to Maturing Achievement and the Disease Picture, *J Clin Investigation* **18** 87-100 (Jan) 1939.

Typhus Fever —The infectious agent of typhus fever was found to persist for a year in the brains of rats¹¹⁷ The brains of rats inoculated with the virus of Rocky Mountain spotted fever were not infectious after a month Endemic typhus fever can be maintained in native field mice¹¹⁸ Gray squirrels, fox squirrels, cottontail rabbits, swamp rabbits, chipmunks and skunks were all found to be susceptible to the virus¹¹⁹ Rats were found to harbor typhus rickettsias (murine form) in North China, where it was previously believed that only the epidemic, or human, form existed¹²⁰ All of these studies emphasize the importance of native rodents as a perennial reservoir of typhus fever

Boston investigators¹²¹ found that by giving typhus-infected rats a diet deficient in riboflavin a greatly increased yield of rickettsias was obtained A reduction of resistance of animals brought about by a diet deficient in riboflavin might be useful in studying other viruses of low invasiveness for otherwise healthy animals

Davis and Cox¹²² recovered from wood ticks a filter-passing agent similar to the one described by Noguchi in 1926 The agent caused disease when inoculated into guinea pigs, and it could be propagated by transfer from one animal to another The virus passes through filters which hold back the rickettsias of typhus and spotted fever, and cross immunity tests failed to show any relationship with these infectious agents The filter-passing agent survived in ticks experimentally infected and in eggs deposited by infected females and was transmitted by the progeny The agent was not a filtrable virus in the strict sense of the term, since numerous minute rickettsia-like organisms were seen

117 Philip, C B, and Parker, R R The Persistence of the Viruses of Endemic (Murine) Typhus, Rocky Mountain Spotted Fever and Boutonneuse Fever in Tissues of Experimental Animals, Pub Health Rep **53** 1246-1251 (July 22) 1938

118 Brigham, G D Endemic Typhus Virus in Mice, *ibid* **53** 1251-1256 (July 22) 1938

119 Brigham, G D Susceptibility of Animals to Endemic Virus, Pub Health Rep **53** 2078-2079 (Nov 25) 1938

120 Wu, C J, and Zia, S H Isolation of Typhus Fever Virus from House Rats in Peiping, Proc Soc Exper Biol & Med **39** 163-165 (Oct) 1938 Liu, W T, and Chung, H L A Murine Typhus Virus Isolated from a Patient in Peiping China, *ibid* **40** 350-353 (March) 1939

121 Pinkerton, H, and Bessey, O A The Loss of Resistance to Murine Typhus Infection Resulting from Riboflavin Deficiency in Rats, Science **89** 368-370 (April 21) 1939

122 Davis, G E, and Cox, H R A Filter-Passing Infectious Agent Isolated from Ticks I Isolation from Dermacentor Andersoni Reactions in Animals, and Filtration Experiments, Pub Health Rep **53** 2259-2267 (Dec 30) 1938 Parker, R R, and Davis, G E II Transmission by Dermacentor Andersoni, *ibid* **53** 2267-2270 (Dec 30) 1938 Cox, H R III Description of Organism and Cultivation Experiments, *ibid* **53** 2270-2276 (Dec 30) 1938 Dyer, R E IV Human Infections *ibid* **53** 2277-2282 (Dec 30) 1938

in stained sections of tissues from infected animals. The stained organisms look like rickettsias of typhus but also resemble *Bartonella bacilliformis* of Carrion's disease. They could not be cultivated on special mediums but were cultivated readily in tissue cultures.

One of the investigators of the disease became ill with malaise, pain in the eyes, chilly sensations, sweating, a temperature which reached 40 C (104 F) and dropped to normal on the seventh day, and pain and swelling in the joints of the fingers. The leukocytes numbered 8,800 per cubic millimeter. Blood from the patient inoculated into guinea pigs caused the same type of reaction as mentioned in a preceding paragraph. Furthermore, the patient's serum during convalescence protected guinea pigs against infection with the agent under study. Dyer suggests that the disease may be identical with the "Q" fever discovered in Australia, which is also transmitted by ticks. Guinea pigs convalescent from "Q" disease were immune to infection with the rickettsia from Montana.

Of interest is a psittacosis-like atypical pneumonia reported by Rasmussen¹²². He studied 68 cases of an epidemic form of pneumonia which occurs occasionally in the Faroe Islands. He believes that a connection exists between the incidence of the disease and the catching of young marine birds, which may be the source of the infection. Pinkerton¹²³ reports an instance of anthrax contracted from minks on a fur farm.

An epidemic of paratyphoid fever broke out in a village in Sweden two weeks after an attack of enteritis in a dog¹²⁴. The dog's blood later was found to agglutinate specifically the suspension of the bacillus. Another epidemic of paratyphoid infection in Sweden was also traced to a dog which came from a village in which the disease was prevalent¹²⁵.

Anderson¹²⁶ believes that hepatitis in man may be acquired by infection from a similar disease in swine. In swine it is an infectious parenchymal hepatic disease transmissible to rats. No experimental data are offered as to the nature of the infectious agent. Dienes¹²⁷ reported an outbreak of hepatitis in Germany.

Ten Broeck and Nelson¹²⁸ discovered a highly fatal disease among guinea pigs in their colony of animals. The causative agent seemed

123 Pinkerton, H. An Outbreak of Anthrax Infection in Minks with Infection of a Ranch Owner, *J. A. M. A.* **112** 1148-1149 (March 25) 1939.

124 Caspersen, J. Ein Hund als wahrscheinliche Infektionsquelle eines kleinen Paratyphus-B-Ausbruches, *Ztschr. f. Hyg. u. Infektionskr.* **120** 611-614 (July) 1938.

125 Magnussen, K. E. Ein Hund als Ansteckungsquelle von Paratyphus-infektion, *Ztschr. f. Hyg. u. Infektionskr.* **121** 136-138 (Oct.) 1938.

126 Anderson, T. T. Investigations on the Etiology of Epidemic Hepatitis, *Ugeskr. f. læger* **100** 777-806 (July 14) 1938.

127 Dienes, H. Hepatitis epidemica in Dossenheim bei Heidelberg, *Ztschr. f. Hyg. u. Infektionskr.* **120** 526-538 (June) 1938.

128 Ten Broeck, C., and Nelson, J. B. A Highly Fatal Disease of Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **39** 572-573 (Dec.) 1938.

to be a filtrable virus. A few young animals became ill, and organ suspensions were injected into other animals. Fever developed after two to five days, leukopenia occurred and the animals given the injections all died in about two weeks. Pneumonia occurred only in animals inoculated intranasally and in those infected by contact. No other lesions were described except enlarged lymph nodes.

Hammon and Enders¹²⁹ isolated a virus from cats during a spontaneous epidemic. The virus caused leukocytosis and intestinal lesions, in which inclusion bodies were present.

A curious form of chronic ulcerative cecitis was observed in rats, characterized by chronic lymphangitis, lymphedema and lymphoid hyperplasia of the lymph nodes of the mesentery.¹³⁰

Sabin¹³¹ subjected tissue infected with *Toxoplasma* to a temperature of -80°C , killing the organisms, and found unexpectedly a filtrable transmissible agent with neurolytic properties for mice to be present. This agent passed through a 720 but not through a 628 millimicron graded collodion membrane. After it had been inoculated intraocularly in mice, films of the inner contents of the eyes, stained by Giemsa's method, revealed peculiar minute structures. Later experiments suggested that this neurolytic agent was similar to that associated with pleuropneumonia and similar to the one isolated by Findlay and Klieneberger from mice during passage of the viruses of yellow fever and lymphocytic choriomeningitis.¹³²

A progressive proliferative polyarthritis with clinical and pathologic similarities to human rheumatoid arthritis was produced experimentally in mice with a filtrable pleuropneumonia-like micro-organism recently isolated from a normal mouse. Sabin¹³³ suggests investigation to determine whether or not a similar agent may play a role in human rheumatoid arthritis.

Andrei and Ravenna¹³⁴ report the development of thromboendocarditis in rabbits after intraperitoneal injection of various substances

129 Hammon, W. D., and Enders, J. F. A Virus Disease of Cats, Principally Characterized by Aleukocytosis, Enteric Lesions and the Presence of Intranuclear Inclusion Bodies, *J. Exper. Med.* **69** 327-351 (March) 1937.

130 Jones, B. F., and Stewart, H. L. Chronic Ulcerative Cecitis in the Rat, *Pub. Health Rep.* **54** 172-175 (Feb. 3) 1939.

131 Sabin, A. B. Isolation of a Filtrable, Transmissible Agent with "Neurolytic" Properties from *Toxoplasma*-Infected Tissue, *Science* **88** 189-191 (Aug. 26) 1938.

132 Sabin, A. B. Identification of the Filtrable, Transmissible Neurolytic Agent Isolated from *Toxoplasma*-Infected Tissue as a New Pleuropneumonia-Like Microbe, *Science* **88** 575-576 (Dec. 16) 1938.

133 Sabin, A. Experimental Proliferative Arthritis in Mice Produced by Filtrable Pleuropneumonia-Like Microorganisms, *Science* **89** 228-229 (March 10) 1939.

134 Andrei, G., and Ravenna, P. Thromboendocarditis in Rabbits. New Disease Due to Infravirus (?), *Arch. Int. Med.* **62** 377-383 (Sept.) 1938.

such as human blood, horse serum and milk. The disease, when established, could apparently be transmitted to other rabbits. The observers believe the causative agent to be a filtrable virus, since cultures made from the lesions were sterile. These observations may be of importance with respect to subacute bacterial endocarditis in human beings.

Pasteurella Infections—Ewing and Fox¹³⁵ report the presence in Iowa, Minnesota, Illinois and Ohio of *Xenopsylla cheopis*, the oriental rat flea capable of transmitting plague. A small epidemic of pneumonic plague broke out in Ecuador in January 1939.

Jellison¹³⁶ calls attention to the importance of flesh-eating birds as disseminators of plague. Predatory birds often carry flea-bearing carcasses of small animals great distances and may serve as accidental hosts to fleas of rodents which transmit plague. Casts of birds fed with plague-infected animal tissue were consistently infectious.

Topping, Watts and Lillie¹³⁷ report the first case to be recorded in English or American literature of human infection with *Pasteurella pseudotuberculosis rodentium*, a bacterium associated with disease in animals, particularly rodents. The germ belongs to the *Pasteurella* group and is closely related to *Pasteurella pestis* of plague and to *Pasteurella tularensis*, as I pointed out in 1931. Unfortunately, the confusing term "pseudotuberculosis" was given to the disease. It has no relation to tuberculosis or to Besnier-Boeck disease or to many other conditions which have been called pseudotuberculosis only because of the presence of minute granulomatous lesions. Plette¹³⁸ in Holland described a case of pasteurellosis but failed to classify it further.

BACILLARY DISEASES

Undulant Fever—The cause of the serious epidemic of undulant fever which broke out among students in East Lansing, Mich.,¹³⁹ was traced to defective plumbing and a faulty sterilizer in the bacteriologic laboratory. Back-siphonage of incompletely sterilized waste caused the distribution of contaminated water in the building. The situation is reminiscent of the outbreak of amebic dysentery in Chicago as a result of similar defects of plumbing.

135 Ewing, H. E., and Fox, I. Occurrence of the Oriental Rat Flea in the Interior of the United States, *Science* **88** 427 (Nov. 4) 1938.

136 Jellison, W. L. Sylvatic Plague. Studies of Predatory and Scavenger Birds in Relation to Its Epidemiology, *Pub. Health Rep.* **54** 792-798 (May 12) 1939.

137 Topping, N. H., Watts, C. E., and Lillie, R. D. A Case of Human Infection with *B. Pseudotuberculosis Rodentium*, *Pub. Health Rep.* **53** 1340-1352 (Aug. 5) 1938.

138 Plette, J. G. Pasteurellose bij den mensch, *Nederl. tijdschr. v. geneesk.* **82** 6106-6110 (Dec. 24) 1938.

139 *Medical News*, *J. A. M. A.* **112** 653 (Feb. 18) 1939.

According to Evans, Robinson and Baumgartner,¹⁴⁰ at the National Institute of Health, no single test other than the isolation of *Brucella* from the patient can be relied on with certainty for diagnosis. The blood of 4 of 7 patients from which *Brucella* was isolated gave a negative agglutination reaction. A negative agglutination reaction cannot be regarded as evidence against infection, but a positive reaction indicates the presence of latent or active infection. A positive skin test is less reliable than a positive agglutination test, and the opsonocytophagic test is least reliable of all. All three tests gave negative results in 3 proved cases of brucellosis. Calder, Steen and Baker¹⁴¹ point out the constancy of the normal or low leukocyte count and of active lymphocytosis in brucellosis. In my experience, the low leukocyte count and relative or absolute lymphocytosis were the most constant of various laboratory observations among 30 patients with the disease.

Tuberculosis—The controversy concerning the value or the harm of hypersensitivity in tuberculosis is still unsettled. Different investigators, using different methods, come to opposite conclusions. For example, Willis and his group¹⁴² find that desensitized guinea pigs have extensive infections. Animals never permitted to become allergic die from tuberculosis before the control animals. According to Freund and Opie,¹⁴³ animals sensitized and immunized are more resistant to infection, but there is no correlation between the intensity of sensitization or the titer of antibodies and resistance to infection. Follis,¹⁴⁴ on the other hand, shows that animals infected with tubercle bacilli and prevented from becoming hypersensitive show less caseation than animals that become hypersensitive. Corper and Cohn¹⁴⁵ point out the striking difference between the specific immune and the accompany-

140 Evans, A. C., Robinson, F. H., and Baumgartner, L. Studies on Chronic Brucellosis. IV. An Evaluation of the Diagnostic Laboratory Tests, *Pub. Health Rep.* **53** 1507-1525 (Aug. 26) 1938.

141 Calder, R. M., Steen, C., and Baker, L. Blood Studies in Brucellosis, *J. A. M. A.* **112** 1893-1898 (May 13) 1939. Munger, M., and Huddleson, T. F. A Preliminary Report of the Blood Picture in Brucellosis, *J. Lab. & Clin. Med.* **24** 617-619 (March) 1939. Schmid, N. Blood and Bone Marrow in Bang's Disease (*Brucella abortus* Infection), *Schweiz. med. Wchnschr.* **69** 191-192 (March 4) 1939.

142 Willis, H. S., Woodruff, C. E., Kelly, R. G., and Voldrick, M. Allergic and Desensitized Guinea Pigs, *Am. Rev. Tuberc.* **38** 10-26 (July) 1938.

143 Freund, J., and Opie, E. L. Sensitization and Antibody Formation with Increased Resistance to Tuberculous Infection Induced by Heat Killed Tubercle Bacilli, *J. Exper. Med.* **68** 273-298 (Aug.) 1938.

144 Follis, R. H. The Effect of Preventing the Development of Hypersensitivity in Experimental Tuberculosis, *Bull. Johns Hopkins Hosp.* **63** 283-304 (Nov.) 1938.

145 Corper, H. J., and Cohn, M. I. The Effects of Tuberculoprotein, *J. A. M. A.* **112** 403-408 (Feb. 4) 1939.

ing allergic features of tuberculosis, the former giving protection and the latter giving a peculiar form of intoxication

Feldman and Baggenstoss¹⁴⁶ examined encapsulated, caseous or calcified areas in the pulmonary tissues or tracheobronchial lymph nodes from 68 patients who died from causes other than tuberculosis. Tubercle bacilli were found in only a single instance. The authors believe that the "primary complex" in most cases of healed tuberculosis in adults seldom contains viable tubercle bacilli and that endogenous infection is unlikely to occur from old capsulated or calcified areas.

Seibert, Pedersen and Tiselius¹⁴⁷ applied the Svedberg ultracentrifuge in studies on the chemical and physical nature of tuberculin.

McKinney and Mellon¹⁴⁸ report derivation of the mucoid (M) phase of *Mycobacterium tuberculosis* (H-37) in cultures in alkaline neopeptone glycerol broth.

Myers¹⁴⁹ defends his methods of detecting tuberculosis against the unfavorable views of Lumsden. The tuberculin test, when performed properly, is of great assistance in recognizing this disease. Unfortunately, like other tests applied to the skin, it is occasionally unreliable, but the number of cases in which it fails to indicate tuberculosis is insignificant as compared with the number in which it is positive. Roentgenograms, he points out, are highly unreliable in making an etiologic diagnosis. It is impossible to differentiate shadows cast by bone, calcium and dense fibrous tissue, respectively, and other conditions besides tuberculosis may cause calcification in the lungs, about 12 per cent of tuberculous areas may be obscured by the heart, diaphragm and other opaque parts, early tuberculous lesions may be microscopic in size, and a number of other possibilities make up an 80 per cent handicap for roentgenographic examination as a method of diagnosis.

Myer's views concerning the shortcomings of roentgenographic diagnosis could, I believe, be extended to other fields. As I stated at the May 1938 meeting of the American Medical Association, roentgenologists often exceed their limitations when they report as an "abscess" an area of rarefaction about the root of a tooth or as

146 Feldman, W. H., and Baggenstoss, A. H. The Residual Infectivity of the Primary Complex of Tuberculosis, *Am J Path* **14** 473-490 (July) 1938.

147 Seibert, F. B., Pedersen, K. O., and Tiselius, A. Molecular Weight, Electrochemical and Biological Properties of Tuberculin Protein and Polysaccharide Molecules, *Am Rev Tuberc* **38** 399-409 (Oct) 1938.

148 McKinney, R. A., and Mellon, R. R. Variability of Tubercle Bacilli. I. Mucoid Phase of the Human Type Strain H-37, *Proc Soc Exper Biol & Med* **40** 298-301 (Feb) 1939.

149 Myers, J. A. The Detection of Tuberculosis, *J A M A* **112** 1904-1910 (May 13) 1939.

"sinusitis" a cloudiness of one or more of the nasal accessory sinuses. It is impossible on the basis of rarefaction or shadows without clinical symptoms or signs to determine the presence or absence of infection with certainty, and many unnecessary operations, I believe, have been performed on such weak evidence. A diagnosis should be arrived at only after complete study with all the means available, of which roentgenography is only one, but a valuable one when properly used.

Bacillary Dysentery—Brown and Barger¹⁵⁰ studied 140 patients who had had bacillary dysentery in an epidemic sixteen years ago to find whether ulcerative colitis was a common sequel. Of the patients who could be traced, 77 had not had any symptoms of bowel trouble since their attack, and only 1 had chronic ulcerative colitis, although 45 still had Shiga dysentery bacilli in the stool. The evidence does not favor the view that acute bacillary dysentery is a common precursor of chronic ulcerative colitis.

Schiff¹⁵¹ describes a few cases of infection among children in which a "new" type of so-called paratyphoid bacilli, namely, "*Salmonella Panama*," was isolated. The "paratyphoid bacilli" commonly cause food poisoning. The three main types of this group of bacilli are *Bacterium*, or *Salmonella*, aertryke, *Bacterium*, or *Salmonella*, enteritidis and *Bacterium*, or *Salmonella*, supestrifer. It appears that, as in the case of pneumococcus, many other types may exist, of which the type Panama may be one. The bacillus was first isolated by Jordan from soldiers suffering from food poisoning in Panama and was identified by Kauffmann in Copenhagen.

Felsen and Osofsky¹⁵² suggest that acidity of the stomach is an effective barrier against infections with dysentery bacilli. Filtered gastric juice of p_H 5.5 or less is bactericidal for Duval-Sonne dysentery bacilli.

Note is made^{152a} of the relative absence of acute amebic dysentery in persons unusually exposed to infection. It is probable that some degree of immunity may be acquired as a result of repeated exposure to amebic infection or that various strains of *Endamoeba histolytica* differ in their invasiveness.

150 Brown, P. W., and Barger, J. A. Bacillary Dysentery. Late Results and Relationship to Chronic Ulcerative Colitis, *Am J Digest Dis* **5** 562-565 (Nov.) 1938.

151 Schiff, F. *Salmonella Panama*. Occurrence in Serious Infections of Infants in New York City, *J A M A* **111** 2458-2460 (Dec 31) 1938.

152 Felsen, J., and Osofsky, A. G. Gastric Barrier in Bacillary Dysentery, *Arch Int Med* **63** 64-70 (Jan.) 1939.

152a Spector, B. K., Hardy, A. V., and Mack, M. G. Studies of the Acute Diarrheal Diseases, *Pub Health Rep* **54** 1105-1113 (June 23) 1939.

Tetanus—Extensive research on tetanus by Abel and his associates¹⁵³ during the past few years led to the impression that the incidents which occurred during the first few hours after infection determined whether the disease would end in death or recovery. From animal experiments it seemed that no amount of antitoxin injected after the toxin once became fixed to nerve tissue would be of any avail in preventing death. Because of subsequent experiments made before Abel's death, this view had to be modified. Although large amounts of antitoxin will not save an animal given a lethal injection of toxin if the delay is too long or if symptoms of descending tetanus have begun, it is still obligatory for physicians to use antitetanic serum in accordance with present usage. In dealing with tetanus in man as compared with experimentally infected animals none of the factors are under control, and there is no way of learning whether a lethal dose of toxin has been fixed or not. It is not known how rapidly or how long toxin is formed at the site of infection. Contrary to general belief,^{153a} the timely injection of a large amount of antitetanic serum neutralizes fixed toxin and prevents it from exerting its usual fatal action. In animals, after injection of from 3 to 10 lethal doses of toxin the period in which neutralization of toxin and saving of life may be accomplished lasts from forty to twenty-four hours, depending on the amount of toxin injected. In all cases, however, antitoxin given after the period of incubation has merged into the period of onset of symptoms fails to save life. Antitetanic serum is therefore not entirely devoid of curative properties, provided it is given in large amounts as soon as possible after infection.

Another interesting feature is that biologic assays made of spinal cords after they have "fixed" the toxin give no indication of its presence, suggesting that it has been chemically bound, changed or denatured.^{153b} Abel^{153c} defends his theory against Doerr's criticism and shows beyond doubt that tetanus toxin is carried to the central neurons by way of the blood stream and not by way of the axis-cylinders of motor nerves.

153 (a) Abel, J. J., Hampil, B., Jonas, A. F., Jr., and Chalian, W. *Researches in Tetanus*. VII (1) The Time Required for the Fixation of a Fatal Quantity of Tetanus Toxin, (2) The Return Passage of Toxin by Way of the Lymphatic Capillaries to the Cardiovascular System, (3) The Return Passage as the Basis of a Method for the Approximate Determination of the Volume of Lymph in the Closed Lymphatic System, *Bull. Johns Hopkins Hosp.* **62**: 522-563 (May) 1938. (b) Abel, J. J., Firor, W. M., and Chalian, W. *Researches on Tetanus*. VIII. At What Point in the Course of Tetanus Does Antitetanic Serum Fail to Save Life? *ibid.* **62**: 610-633 (June) 1938, (c) IX. Further Evidence to Show that Tetanus Toxin Is Not Carried to Central Neurons by Way of the Axis Cylinders of Motor Nerves, *ibid.* **63**: 373-403 (Dec.) 1938.

Hertz¹⁵⁴ reports 3 cases of failure of tetanus antitoxin used prophylactically to save life. In another case tetanus bacilli were found in a scar ten years after an attack of the disease¹⁵⁵

COCCAL DISEASES

Subacute Bacterial Endocarditis—Poston and Orgain¹⁵⁶ were unable to demonstrate any significant specific serologic evidence of immunity in patients during the active bacteremic stage of any type of endocarditis, including that caused by *Streptococcus viridans*. Immune bodies developed coincidentally with the disappearance of bacteremia. Their work has raised the perennial question as to the actual relation of streptococci to the disease. Despite the frequent association of *Str viridans* with the disease, numerous observers, including myself, have suspected that some other agent may be the underlying cause, the streptococcus being a secondary invader. *Str viridans* has not yet been conclusively shown to be a primary cause of any disease. Its mere presence in a diseased area does not prove its pathogenicity.

According to Moran,¹⁵⁷ the physiologic and fermentative reactions of streptococci from 20 patients with endocarditis permit their classification as members of the group of "salivary" streptococci or enterococci. This suggests that the streptococci concerned came from an endogenous source—somewhere in the respiratory tract or gastrointestinal tract.

Staphylococcus Osteomyelitis—Thompson and Dubos¹⁵⁸ succeeded in causing osteomyelitis in rabbits by injecting a culture of a *Staphylococcus* intravenously. When large amounts of culture were injected, infection was apt to be fulminating and to end in early death. The injection of small amounts in normal rabbits or of large amounts in rabbits previously immunized was followed by a more chronic type of infection. Of 31 rabbits studied, a prolonged illness of one to three weeks was established in 22, and in 18 of these osteomyelitis developed. There was a predilection of the bacteria for the metaphyses of the long

154 Hertz, J. Failure of Tetanus Prophylaxis, *Ugeskr f læger* **100** 871-877 (Aug 4) 1938.

155 Bonney, V., Box, C., and MacLennan, J. Tetanus Bacilli Recovered from the Scar Ten Years After an Attack of Postoperative Tetanus, *Brit M J* **2** 10-11 (July 2) 1938.

156 Poston, M., and Orgain, E. S. Immunologic Studies on Patients Suffering from Bacterial Endocarditis, *Proc Soc Exper Biol & Med* **40** 284-286 (Feb) 1939.

157 Moran, H. Classification of Streptococci from Cases of Endocarditis, *Proc Soc Exper Biol & Med* **38** 805-808 (June) 1938.

158 Thompson, R. H. S., and Dubos, R. J. Production of Experimental Osteomyelitis in Rabbits by Intravenous Injection of *Staphylococcus Aureus*, *J Exper Med* **68** 191-206 (Aug) 1938.

bones, similar to that which is commonly observed in children. Multiple abscesses of the kidneys were present in most of the animals.

Meningitis—Cowan,¹⁵⁹ studied bacteria isolated from cerebral infections in 5 patients on whom operations were performed. Atypical gram-positive or gram-negative bacilli and a gram-negative capsulated coccus were recovered. These bacteria would ordinarily be regarded as saprophytes or contaminants, but he believes that they actually caused infection of the brain because of their placement in sites ordinarily never exposed to bacteria. The coccus which was isolated was thought to be the same as *Diplococcus mucosus* of von Lingelsheim. It has certain resemblances to atypical gram-negative cocci which Koucky and I obtained from a patient with meningitis.¹⁶⁰

OTHER DISEASES

Infectious Diseases of the Gastrointestinal Tract of Unknown Origin—Boardman¹⁶¹ reports a fairly widespread outbreak of acute gastroenteritis in San Francisco. The disease was characterized by an acute and sudden onset of nausea, abdominal cramps, watery diarrhea, sometimes vomiting, slight headache, general aching, dizziness and fever occasionally as high as 40 C (104 F). In some cases there was evidence of an infection of the upper portions of the respiratory tract a day or two before the onset of general symptoms. The leukocyte counts varied from 10,100 to 20,000. Bacilli of the typhoid-dysentery group were isolated from 10 of 28 patients, but Boardman does not feel convinced of their etiologic significance. He calls attention to the frequency of similar outbreaks of gastrointestinal disease in sporadic or epidemic form elsewhere and suggests that defective plumbing may be responsible for its spread. He suggests that the infection may be caused by a filtrable virus, which may also be carried in the secretions of the nose and throat. A similar disease was described by Spencer in 1930 and by Willman in 1933, and one occurred in Chautauqua County, N. Y., in March 1939.

A supposedly "new" disease, called epidemic nausea and vomiting, has been noted in Europe since 1935.¹⁶² It may be the same as that recorded by Boardman and others. The illness is mild, seldom lasts longer than forty-eight hours and is characterized by nausea, vomiting,

159 Cowan, S. T. Unusual Infections Following Cerebral Operations, *Lancet* **2** 1052-1054 (Nov. 5) 1938.

160 Reimann, H. A., and Koucky, R. W. Meningitis Caused by Atypical Gram-Negative Cocci, *J. Bact.* **37** 401-410 (April) 1939.

161 Boardman, W. W. Acute Infectious Gastro-Enteritis, *Am. J. M. Sc.* **196** 833-840 (Dec.) 1938.

162 Gray, J. D. Epidemic Nausea and Vomiting, *Brit. M. J.* **1** 209-211 (Feb. 4) 1939.

giddiness, slight fever and diarrhea. Such epidemic illnesses are perhaps very common but because of their mildness and brief duration are seldom studied carefully or are mistaken for bacillary dysentery or food poisoning.

A mild epidemic disease called vesicular pharyngitis and stomatitis affected 106 persons in a boys' camp¹⁶³. Vesicles of the faucial pillars, soft palate and tonsillar tissue and fever were the chief signs, and headache, malaise and sore throat were the chief symptoms. On clinical evidence alone it was suggested that the disease was of herpetic origin.

Ulcerative Colitis—Three papers¹⁶⁴ on ulcerative colitis leave one with a rather pessimistic attitude as far as knowledge of the cause of the disease or successful management or prevention of it is concerned. Mackie^{164a} did not observe much, if any, benefit after the use of vaccines, antisera, bacteriophage or surgical procedures. Jones^{164b} is not enthusiastic about surgical treatment except when only the left half of the colon is diseased. Willard and his associates^{164c} find that no single therapeutic measure produces striking results and that often the entire alimentary tract fails to influence the course. In their experience surgical intervention was accompanied by a death rate of 73 per cent.

In a discussion of these three papers Bloomfield points out an interesting analogy of ulcerative colitis with several other diseases of a seminflammatory-semidegenerative nature, namely, iritis, choroiditis, arthritis and hepatitis, in the study of which little or no progress in knowledge has been made. Aaron, discussing the striking effects claimed to occur after liver preparations have been given to patients, stated that this treatment merely corrects the dietary deficiency which may follow injudicious restriction of food.

Acute Rheumatic Fever—Many papers on rheumatism and arthritis were discussed by Hench and his associates¹⁶⁵ in their fifth annual review of rheumatism and need not be referred to again here.

163 Levine, H. D., Hoerr, S. O., and Allanson, J. C. Vesicular Pharyngitis and Stomatitis. An Unusual Epidemic of Possible Herpetic Origin, *J. A. M. A.* **112** 2020-2022 (May 20) 1939.

164 (a) Mackie, T. T. The Medical Management of Chronic Ulcerative Colitis, *J. A. M. A.* **111** 2071-2076 (Dec 3) 1938. (b) Jones, T. E. The Surgical Treatment of Ulcerative Colitis, *ibid.* **111** 2076-2078 (Dec 3) 1938. (c) Willard, J. H., Pessel, J. F., Hundley, J. W., and Bockus, H. L. The Prognosis of Ulcerative Colitis, *ibid.* **111** 2078-2084 (Dec 3) 1938.

165 Hench, P. S., Bauer, W., Dawson, M. H., Hall, F., Holbrook, W. P., and Key, J. A. The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1937, *Ann. Int. Med.* **12** 1005-1104 (Jan.), 1295-1374 (Feb.) 1939.

Eagles and his associates¹⁶⁶ were unable to show that the virus-like bodies suspected of causing rheumatic fever were pathogenic for animals. Keil¹⁶⁷ made a critical review of papers pertaining to the subcutaneous nodule of rheumatism. He believes, as I do, that although the lesions in acute rheumatic fever may resemble histologically those found in rheumatoid arthritis, they need not be considered identical. It seems unsafe to establish the etiologic identity of two diseases on the basis of histologic changes when the clinical differences are usually so distinctive.

Salvesen¹⁶⁸ found nephritis to follow acute rheumatic fever in 47 per cent of 212 cases. He describes in detail 6 cases in which nephritis supposedly was the result of rheumatic fever.

Rheumatic pericarditis was found to be far less serious than rheumatic valvulitis¹⁶⁹.

Swift and Brown¹⁷⁰ introduced exudates from patients with rheumatic fever onto chorioallantoic membranes, intranasally into mice and intraocularly into rabbits. Characteristic lesions developed in mice as pneumonia and in rabbits as iritis. From these lesions a filtrable organism was obtained which produced a pleuropneumonia-like illness in animals. Similar material obtained from nonrheumatic patients failed to cause lesions or to show any unusual organisms. The etiologic significance of this discovery in respect to the cause of rheumatic fever is under study.

Malaria—Investigators in the Southern States are finding an acridine derivative (atabrine) of value in the control of malaria¹⁷¹. Cures in 90 per cent of the patients are claimed. One study showed the

166 Eagles, G. H., Evans, P. R., Fisher, A. G. T., and Keith, J. D. Infection Experiments with Virus-like Bodies from Rheumatism, *J. Path. & Bact.* **46** 481-495 (May) 1938.

167 Keil, H. Rheumatic Subcutaneous Nodules and Simulating Lesions, *Medicine* **17** 261-380 (Sept.) 1938.

168 Salvesen, H. A. Rheumatic Fever and Nephritis, *Acta med. Scandnav.* **96** 304-314 (Sept. 3) 1938.

169 Massie, E., and Levine, S. A. The Prognosis and Subsequent Developments in Acute Rheumatic Pericarditis, *J. A. M. A.* **112** 1219-1223 (April 1) 1939.

170 Swift, H. F., and Brown, T. M. Pathogenic Pleuropneumonia-like Microorganisms from Acute Rheumatic Exudates and Tissues, *Science* **89** 271-272 (March 24) 1939.

171 Hill, R. A., and Goodwin, M. H. Two Years' Observation on the Use of Atabrine as Prophylactic Agent in Malaria, *Am. J. Trop. Med.* **18** 339-346 (July) 1938. Holton, C. F., and Winchester, M. E. Use of Atabrine in the Treatment and Control of Malaria Among a Group of Industrial and Agricultural Employees in Georgia, *J. M. A. Georgia* **27** 299-303 (Aug.) 1938. Gill, D. G., and Smith, M. Atabrine as Malarial Prophylactic Agent. Experiment with Drug in a Region in Central Alabama, *J. M. A. Alabama* **8** 66-67 (Aug.) 1938.

blood parasite index reduced from 16.9 to 0.3 per cent after two years of prophylaxis with this drug. Proske and Watson¹⁷² have devised a test for malaria based on a protein tyrosine reaction of the serum. The test is based on the chromogenic property of the protein, which can be measured against the color given by tyrosine in the presence of a phenol reagent. The tyrosine index for euglobulin in normal blood serum tests between 50 and 80 while that of serum from patients with malaria is increased from 80 to 280 or more. The test is not strictly specific for malaria, but a positive reaction is present in so many cases of this infection as to make it a valuable diagnostic aid.

Kitchen, Webb and Kupper¹⁷³ studied the effect of malaria on the development of the Wassermann reaction in nonsyphilitic patients. Positive reactions were obtained in every case. The reaction developed usually in the third and fourth week after infection and lasted more than three to four weeks in nearly half the patients studied.

When *Plasmodium vivax* and *Plasmodium malariae* were inoculated together for the treatment of dementia paralytica in 16 patients, both types of parasites were found in the blood, but soon one or the other became dominant.¹⁷⁴ *P. vivax* was usually more successful in surviving. The authors suggest that in many more cases of naturally acquired disease than is believed the infection is of the mixed type.

Yellow Fever—Two varieties of mosquitoes besides *Aedes aegypti* may transmit jungle yellow fever.¹⁷⁵ New Jersey mosquitoes were also found to be capable of transmitting the disease to monkeys.¹⁷⁶ Because of rapid transportation by air from South America, the director of health in Miami, Fla., has ordered all persons who have been in areas that are actually or potentially centers of yellow fever to report within twenty-four hours after arrival and be kept under surveillance for six days.¹⁷⁷ In one study, however, no live mosquitoes

172 Proske, H. O., and Watson, R. B. The Protein Tyrosin Reaction. A Biochemical Diagnostic Test for Malaria, Pub Health Rep **54** 158-172 (Feb. 3) 1939.

173 Kitchen, S. F., Webb, E. L., and Kupper, W. H. The Influence of Malarial Infections on the Wassermann and Kahn Reactions, J. A. M. A. **112** 1443-1449 (April 15) 1939.

174 Mayne, B., and Young, M. D. Antagonism Between Species of Malaria Parasites in Induced Mixed Infections, Pub Health Rep **53** 1289-1291 (July 29) 1938.

175 Shannon, R. C., Whitman, L., and Franca, M. Yellow Fever Virus in Jungle Mosquitoes, Science **88** 110-111 (July 29) 1938.

176 Bennett, B. L., Baker, F. C., and Sellards, A. W. The Behavior of the Virus of Yellow Fever in the Mosquito, *Aedes Triseriatus*, Science **88** 410-411 (Oct. 28) 1938.

177 Miami Health Officer Acts to Prevent the Introduction of Yellow Fever. Pub Health Rep **53** 1621 (Sept. 9) 1938.

of the species *Aedes aegypti* were found on incoming aircraft in 1938, but several other varieties, both alive and dead, were ¹⁷⁸

The Rockefeller Foundation,¹⁷⁹ in cooperation with the Brazilian government, has vaccinated over 1,000,000 persons against yellow fever. Among those vaccinated, 8 contracted yellow fever, 6 of them within four days of vaccination. Local physicians reported a sudden reduction in number of cases shortly after the mass vaccination.

Emmons¹⁸⁰ observed a species of *Actinomyces* in 37 per cent of 200 pairs of tonsils removed from patients for other reasons. It seems probable that these fungi are commonly present in normal mouths and throats.

McMaster and Gilfillan¹⁸¹ report 24 cases of osteomyelitis caused by *Coccidioides*.

Pons and Julianelle¹⁸² isolated *Listerella monocytogenes* from the blood of a patient with infectious mononucleosis. The bacterium when injected into rabbits caused characteristic lymphocytic-monocytic changes. Schultz, Terry and Brice¹⁸³ suggest that *Listerella monocytogenes* may be a cause of meningoencephalitis in man. It must be decided, of course, whether this bacterium was the cause of the conditions in patients from whom it was recovered or whether it was merely a saprophyte.

MISCELLANEOUS STUDIES

Diesel¹⁸⁴ apparently caused transformation in the test tube of non-pathogenic *Bacterium typhi flavum* into virulent typhoid bacilli. The interpretation of his work as type transformation has support in observations reported in 1938 in which similar changes from chromogenic bacteria to nonchromogenic ones were reported¹⁸⁵. In a similar vein,

178 Welch, E. V. Insects Found on Aircraft at Miami, Fla., in 1938, Pub Health Rep **54** 561-566 (April 7) 1939.

179 Fosdick, R. B. The Rockefeller Foundation. A Review for 1938, New York, The Rockefeller Foundation, 1939, p. 12.

180 Emmons, C. W. The Isolation of *Actinomyces Bovis* from Tonsillar Granules, Pub Health Rep **53** 1967-1975 (Nov. 4) 1938.

181 McMaster, P. E., and Gilfillan, C. Coccidioidal Osteomyelitis, J. A. M. A. **112** 1233-1237 (April 1) 1937.

182 Pons, C. A., and Julianelle, L. A. Isolation of *Listerella Monocytogenes* from Infectious Mononucleosis, Proc Soc Exper Biol & Med **40** 360-361 (March) 1939.

183 Schultz, E. W., Terry, M. C., Brice, A. T., Jr., and Gebhardt, L. P. *Listerella Monocytogenes*. A Cause of Meningoencephalitis in Man, Proc Soc Exper Biol & Med **38** 605-608 (June) 1938.

184 Dresel, E. G., and Graf, W. Neue Ergebnisse über das Bact. typhi flavum, Arch f Hyg **119** 153-167, 1937.

185 Reimann, H. A. The Significance of Bacterial Type Transformation in Infectious Disease and Epidemiology, Tr. A. Am. Physicians **53** 270-273, 1938.

Horgan¹⁸⁶ reports the transformation of variola to vaccinia virus by passage of the former intratesticularly in rabbits Findlay and MacCallum¹⁸⁷ report further studies on the transformation of a neurotropic strain of yellow fever virus into a pantropic one Each of these observations suggests that type transformation may be a natural phenomenon among bacteria and viruses

Cold Vaccines—The study of Diehl and his associates¹⁸⁸ on the use of vaccines in the prevention or the treatment of colds is of great value in combating many claims by commercial concerns which sell the so-called "cold vaccines" In carefully controlled work it was shown that vaccines taken orally were of no value whatever, vaccines injected subcutaneously seemed to reduce the incidence of colds about 25 per cent, which is not sufficiently great to justify the time and expense of vaccination There was no evidence that vaccines reduce the incidence of complications of colds The results of others¹⁸⁹ are in agreement

Similar conclusions were made by Bock,¹⁹⁰ who studied 1,667 cases of acute infection of the respiratory tract In his cases fatigue of body and mind was an important factor in precipitating such infections He advises against the use of energetic local treatment, which may aggravate and prolong the illness

Jefferson Hospital

186 Horgan, E S The Experimental Transformation of Variola to Vaccinia, J Hyg **38** 702-715, 1938

187 Findlay, G M, and MacCallum, F O Spontaneous Variation in the Neurotropic Strain of Yellow Fever Virus, Brit J Exper Path **19** 367-442 (Dec) 1938

188 Diehl, H S, Baker, A B, and Cowan, D W Cold Vaccines An Evaluation Based on a Controlled Study, J A M A **111** 1168-1173 (Sept 24) 1938

189 Hauser, I J, and Hauser, M J Controlled Study of "Cold Vaccines," Arch Otolaryng **29** 704-719 (April) 1939

190 Bock, A V Clinical Observations, Complications and Treatment of Acute Upper Respiratory Tract Infections, Ann Int Med **12** 317-322 (Sept) 1938

Book Reviews

Rheumatische Kreislaufschädigungen By Dr Siegfried Dietrich Price, 675 marks, unbound Pp 204 Dresden Theodor Steinkopff, 1938

This volume is the seventh of a series dealing with the problem of rheumatism recently published in Germany under the editorship of Prof Rudolph Jurgens. The appearance of the series, according to the editor, is a response to recent recognition among both political and medical circles in the German Reich of the enormous sociologic problem arising from rheumatic diseases. Each volume is intended to present to the practitioner a single facet of this problem in a unified manner.

The book is a reasonably thorough review of well grounded and generally accepted data with regard to the rheumatic state, and the author has included a presentation of much important recent literature dealing with studies of etiologic factors, histopathologic picture, natural history of the disease, modern diagnostic methods and recent views on drug therapy. A carefully compiled bibliography increases the value of the book as a reference tool.

The author has forcefully indicated how preoccupation with isolated features of rheumatic fever, such as chorea, acute arthritis or physical signs of chronic valvular disease, may detract from appreciation of the nature of the diffuse process which constitutes the rheumatic state. The great importance of the myocardial lesion is well stressed. The early clinical phenomena of rheumatic fever are carefully described in an effort to encourage earlier recognition and more adequate early treatment. Lengthy discussions of the end product of rheumatic fever, the failing heart resulting from mechanical impediments of deformed valves, are avoided.

Although the subject matter is generally treated objectively, the author appears to be personally committed on several points in which he is probably in error. Thus, Dietrich has accepted the existence of a chronic inflammatory disease of the heart arising from focal infection, citing the literature which is said to establish the pathologic and clinical features of this disease, tuberculous rheumatoid arthritis is considered by him to be an established entity which must be included in differential diagnosis of rheumatic fever, he believes that chronic progressive deforming arthritis may at times be due to rheumatic fever, a specific disease of the coronary arteries due to rheumatic fever and leading to infarction of the heart is likewise discussed in the text. In the sections concerned with prevention the author urges a rigorous life filled with exercise calculated to harden the body, and even active army service or "work-service" is said to be useful for preventing rheumatic fever. The importance of better housing, sanitation, warmth and sufficient food does not appear to be adequately stressed.

The book is, nevertheless, a rather conservative presentation of current knowledge concerning rheumatic fever. It is clear and thorough and as a source of information on this disease is fairly complete.

Malignant Tumors of the Skeletal Muscles, Fasciae, Joint Capsules, Tendon Sheaths and Serous Bursa Acta radiologica, Supplement 36
By Gunnar Jonsson Pp 304, with 20 illustrations Stockholm P A Norstedt & Son, 1938

This treatise reviews in a concise and well presented manner the material at Radiumhemmet, the literature and a historical sketch of the present knowledge concerning malignant tumors of muscle and fascial sheaths as well as those of joint capsules, tendon sheaths and serous bursae. The author has clearly demonstrated the inadequacies of a histologic classification of such tumors and has emphasized that in spite of existing hiatuses in the knowledge, a histogenetic classification together with topographic considerations lends itself to greater accuracy in foretelling the behavior of a given tumor in selecting the most appropriate type of therapy and in establishing an intelligent prognosis. Dr Jonsson's

historical sketches do much to elucidate the existing chaos of nomenclature. Excellent series of case histories supplemented by numerous photomicrographs illustrate the various types of tumor.

The analysis of the material at Radiumhemmet, though not extensive enough for statistical study, is of interest. This material was divided into two main groups: (a) malignant muscular and fascial tumors and (b) malignant synovial tumors. The malignant muscular and fascial tumors showed the following histologic types: rhabdomyosarcoma, spindle cell sarcoma, fibrosarcoma, myxoliposarcoma and round cell sarcoma. The malignant synovial tumors were divided into the two groups of synovialoma and synovial fibrosarcoma.

The results obtained from the author's study are significant. In a series of 38 cases of rhabdomyosarcoma the tumor was characterized by a rapid course, early distant metastases and only slight radiosensitivity. Fifteen cases of spindle cell sarcoma showed a slower course, no development distant metastases until relatively late and not infrequently a pronounced radiosensitivity. As a whole, this group was moderately radiosensitive. In a series of 10 cases of fibrosarcoma the tumor showed slow growth and low degree of radiosensitivity, and it was not clear whether or not metastases ever occurred. In this series the prognosis for the group was excellent, all the patients being alive and well up to the time of the report, the shortest interval being eighteen months.

Adventures in Respiration. Modes of Asphyxiation and Methods of Resuscitation. By Yandell Henderson. Pp 316. Baltimore: Williams & Wilkins Company, 1938.

In this interesting book the author traces the historic milestones leading to the present understanding of the physiology of respiration and discusses the value and rationale of using carbon dioxide in the treatment of various asphyxial states. Arrangement of the subject matter in narrative form, as an adventure of the author in research over a period of years, endows facts and theories with charm and personal interest. The first part of the book is devoted to a consideration of shock, the control of breathing and blood alkalinity and the "fallacy of asphyxial acidosis," in which discussion the conception of "acarbia" as induced by "hyperpnein" is suggested as a substitute for the theory of "acidosis" induced by lactic or other acid. There are several chapters dealing with the physiologic basis of mountain sickness and acclimatization, carbon monoxide asphyxia and asphyxia of the newborn. The therapeutic value and methods of administration of carbon dioxide in these conditions and in anesthesia, atelectasis and pneumonia are described in detail. In a discussion of circulatory failure and asphyxia the author emphasizes the role of muscle tonus in the control of the circulation and postulates that a failure of muscle tonus may be a major cause of failure of the circulation. Some of the theories championed remain controversial, but the facts of normal and disturbed respiration are clearly delineated, and the whole makes stimulating and enjoyable reading. Evidence of the therapeutic efficacy of carbon dioxide is convincingly presented.

Las arritmias en clínica. By Dr. Antonio Battro. Pp 476, with 201 illustrations. Buenos Aires: El Ateneo, 1937.

Dr. Battro has again scored by presenting an excellent book. In this volume he has thoroughly gone into the subject of the arrhythmias from the diagnostic, prognostic and therapeutic standpoints. The general anatomy of the heart and especially the blood supply is well illustrated. His brief discussion of the physiology and the many graphic tracings are both timely and illustrative of the thoroughness with which the subject is presented.

Basically the book is divided into chapters dealing with the arrhythmias under the following headings: (1) chronotropic arrhythmia, (2) bathmotropic arrhythmia, (3) dromotropic arrhythmia, (4) fibrillation and flutter and (5) inotropic arrhythmia.

The bibliography is thorough, covering fifty pages, and includes a large percentage of references to American authors.

Medical Applications of the Short Wave Current By William Bierman, M D Including a discussion of the physical and technical aspects by Myron M Schwarzschild, M A Price, \$5 Pp 379 Baltimore William Wood & Company, 1938

The author presents in this volume the theoretic and practical principles of therapeutic application of the short wave current The text is divided into two parts Part I, consisting of five chapters, is devoted to fundamental considerations, and Part II, containing three chapters, to clinical considerations

Chapter I is devoted to the history of the development of the short wave current and is concise and clear Chapter II, which deals with the physics of the short wave current, was written by a physicist familiar with the medical requirements of short wave therapy This is a valuable contribution to the volume from the point of view of the average physician, as many of the mysteries of the mode of action of short wave therapy are cleared up

The third chapter deals with the determination of temperature in the living human being The physiologic responses of the various organs and systems to local heat and local short wave currents are discussed in chapter IV The injurious effects of this form of therapy are covered in this chapter

The fifth chapter, on the specificity of the short wave current, is of considerable interest While the author believes that the effects of short wave therapy are due solely to the production of heat, full consideration is given to the other theories, especially to that of specificity

Chapter VI considers technic and methods of application of short wave therapy The directions given are clear and complete, and the various applicators employed are well illustrated and carefully described

The clinical applications of this form of therapy in various clinical conditions are discussed in chapters VII and VIII The clinical results to be expected in each condition are also noted Due emphasis is devoted to those clinical conditions in which short wave therapy may prove of no value or may be harmful The contraindications to the use of this therapy are considered at the end of this section

A fairly complete bibliography and index are included, and this work should serve as a valuable reference to any one employing short wave therapy The illustrations are numerous and clear

News and Comment

Central Society for Clinical Research—The twelfth annual meeting of the Central Society for Clinical Research will be held in Chicago, with headquarters at the Drake Hotel, on Nov 3 and 4, 1939 Dr Walter H Nadler is president, Dr Charles A Doan, vice president, and Dr Lawrence D Thompson, secretary-treasurer

RANGE OF NORMAL BLOOD PRESSURE

A STATISTICAL AND CLINICAL STUDY OF 11,383 PERSONS

SAMUEL C ROBINSON, M D

AND

MARSHALL BRUCER

CHICAGO

The determination of blood pressure is the third most important routine physiologic measurement that the modern physician uses with a fine degree of precision. While it does not carry an immediate purpose in cases of acute illness as do the temperature and the pulse, yet for long range evaluation of the health of the average person it is far more significant. No other commonly used test gives such quick and reasonably exact information concerning life expectancy. With added information derived from the life history of the blood pressure and from mortality data a physician should be able to forecast the longevity or the general pathologic tendencies of many of his patients.

There has been a tendency lately to belittle the taking of blood pressure, but with the generally accepted realization that at least one fifth of the population is hypertensive and bears the stigma of an ominous prognosis, the blood pressure becomes a phenomenon of great moment. Heart disease accounts for more deaths in the United States than any other two causes,¹ and, as Cabot² stated "Hypertension is more common than all other forms of heart disease put together." This

From the Department of Medicine, Woodlawn Hospital

Read in part before the Chicago Society of Internal Medicine, Feb 28, 1938

The source material for this study was gathered from records accumulated during the past ten years by the Life Extension Examiners, Chicago, the West Side Y W C A, Chicago, the Student Health Service of the University of Chicago, and the files of private practice. The statistical labor was performed with the aid of the Works Progress Administration.

1 (a) Dublin, L I, and Lotka, A J. Length of Life. A Study of the Life Table, New York, The Ronald Press Company, 1936. (b) White, P D. Heart Disease, ed 2, New York, The Macmillan Company, 1937.

2 Cabot, R. Heart and Diseases, New York, W B Saunders Company, 1926.

is reflected in office practice, in which hypertension is the most common finding³

Not only is the incidence of hypertension in the civilized population extremely high, but the nature of its morbid process is more widespread and deeply rooted than is generally believed by the average practitioner or even by the specialist in disorders of the heart "Idiopathic" or "essential" hypertension, as is implied in its very definition, is supposed to be a syndrome unassociated with discoverable pathologic change. Some look on "essential" hypertension as a vague disease of the peripheral vascular bed. In reality it is a disease involving nearly all the viscera, especially the heart and kidneys. "High blood pressure is more frequently associated with beginning cardiovascular disease than any other discoverable sign," stated Cook⁴. Myocardial failure in most cases is due primarily to hypertension⁵. Fahr^{5b} concluded that "nearly three-fourths of all so-called chronic myocarditis is due to primary hypertension". Levy⁶ stated that hypertension is the most common single etiologic factor in coronary thrombosis. Fahr^{5a} concluded that coronary sclerosis is present in 90 per cent of all patients who die of hypertension, similarly, Bell⁷ found association of coronary sclerosis with hypertension in 75 per cent of cases. Roberts⁸ stated "The higher the tension the more we find diseased hearts". Hay⁹ stated that "the usual termination of high blood pressure is cardiac defeat".

3 (a) Foster, J. H. The Practice of Medicine in China and New England with Observations on Hypertension, *New England J Med* **203** 1073, 1930 (b) Fisher, W. E. Hypotension, *M J Australia* **1** 110, 1935 (c) Blackford, J. M., and Wilkinson, J. N. Hypertension, *Ann Int Med* **6** 54, 1933 (d) Lemann, I. I. Effect of a Long Continued Subtropical Summer on High Blood Pressure, *Am J Trop Med* **12** 331, 1932 (e) Janeway, T. C. A Clinical Study of Hypertensive Cardiovascular Disease, *Arch Int Med* **12** 755 (Dec.) 1913 (f) Alvarez, W. C., Wulzen, R., and Mahoney, L. J. Blood Pressures in Fifteen Thousand University Freshmen, *ibid* **32** 17 (July) 1923

4 Cook, H. W., in discussion on Clark, C. P. Theoretical Study of Blood Pressure and Its Relation to Heart Size, Body Surface Area and Metabolic Rate, *Proc A Life Insur M Dir America* **20** 224, 1934

5 (a) Fahr, G. Heart in Hypertension, *J A M A* **105** 1396 (Nov 2) 1935, (b) Hypertension Heart, Most Common Form of So-Called Chronic Myocarditis, *ibid* **80** 981 (April 7) 1923, (c) Hypertension Heart, *Am J M Sc* **175** 453, 1928 (d) Christian, H. A. Chronic Myocarditis, *Tr A Am Physicians* **33** 67, 1918 (e) Janeway, T. C. Note on Blood Pressure Changes, *Proc Soc Exper Biol & Med* **6** 109, 1909 (f) Rogers, O. H., and Hunter, A. *Proc A Life Insur M Dir America* **10** 43, 1923

6 Levy, R. L. Diseases of Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936

7 Bell, E. T. Text Book of Pathology, ed 3, Philadelphia, Lea & Febiger, 1938

8 Roberts, S. R. A Study of Hypotension, *J A M A* **79** 262 (July 22) 1922

9 Hay, J. The Significance of a Raised Blood Pressure, *Brit M J* **2** 43, 1931

That the kidneys are clinically associated with hypertension was known even before animal experimentation on the ischemic kidney¹⁰ Our own studies, to be published later, show this relation in respect to urinary findings It is thus seen that hypertension is inseparable from cardiac and renal disease In the light of these facts, "the control of hypertension is one of the outstanding challenges of today"¹¹

While the cause, prevention and cure of disease are the ultimate justification for the study of any physiologic measurement, the workers in the laboratories of the basic medical sciences have yet another reason for coming to grips with the question of blood pressure In studying the range of normal human physiologic measurements, such as the basal metabolic rate, blood chemistry values or electrocardiographic records, selection of normal healthy persons is necessary Two criteria are used to select the "normal" healthy person (1) his subjective state and (2) clinical measurements such as determinations of the pulse rate, temperature and blood pressure The subjectively well state of a person, however, may be associated with morbidity, and one is often forced to fall back on simple clinical measurements It is imperative that the physician know the levels at which these measures denote sound health¹² The importance of finally settling the question of normal blood pressure to help unravel the mystery of hypertension is of the greatest moment, for the sake of correct understanding of normal physiology it is of equal importance

It is in point that many authorities prefer not to commit themselves to definite levels of normal pressure, and some of those who do state normal levels show the uncertainty of their commitment by setting their lower limits of hypertension far above their own upper limits of normal pressure, thereby leaving a "no man's range" For example, Stieglitz¹³ stated: "We may consider 140/90 mm as the maximum normal systolic

10 Bell, E T, and Clawson, B J Primary (Essential) Hypertension A Study of Four Hundred and Twenty Cases, *Arch Path* **5** 939 (June) 1928
Moritz, A R Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am J Path* **13** 679, 1937
Riesman, D High Arterial Pressure, High Pressure Hypertrophy of the Heart, *Am J M Sc* **145** 487, 1913

11 Major, R W Chemical Factors Regulating Blood Pressure, *Am J M Sc* **183** 81, 1932

12 This may be pointedly illustrated by a recent electrocardiographic study of the fourth lead (Shapley, R A, and Hollaran, W R The Four Lead Electrocardiogram in Two Hundred Normal Men and Women, *Am Heart J* **2** 325, 1936), in which the selection of normal persons was partially based on a blood pressure range which, as the present study will show, extended into hypertensive levels Surely some of the subjects in that study of the fourth lead were false "normals"

13 Stieglitz, E J Abnormal Arterial Tension, New York, National Medical Book Company, 1935

pressure irrespective of age, and a systolic pressure of 150 mm or more, diastolic of 95 mm or more, constitutes hypertension." What status has the patient with a pressure of 146 systolic and 92 diastolic? There are great confusion and uncertainty about this important physiologic measurement. There is a range of 40 mm between the lowest and the highest upper limit of normal, which, of course, yields a poor definition.¹⁴ The normal has never been clearly and convincingly defined. Allen¹⁵ stated that "the normal blood pressure of the total population, for different ages and sexes, is unknown." With this we agree.

We should like to discuss in some detail the factors which contribute to this uncertainty and discrepancy of authoritative opinion.

1. There are definite reasons for not accepting the levels obtained in the earlier work on blood pressure as normal physiologic levels. Most of the pioneer studies of blood pressure were done by and for insurance companies, and the tables are still accepted in all textbooks as the basis of blood pressure levels. Insurance statisticians did not set out to make contributions to human physiology; they were interested in the range of blood pressure in which they could establish a profitable insurance premium. Hunter,¹⁶ actuary of the New York Life Insurance Company, stated

The investigations undertaken by the companies were primarily intended to assist them in determining which types of persons [also which levels of pressure] could safely be accepted for insurance at the regular rates of premium, which types should be charged an extra premium, and which should be declined. The purpose of the preparation of these statistics was not to excite public interest or curiosity, but for actual use in a great business.

2. Further, in medical research and among clinicians who deal every day with high and low pressures, the viewpoint has been taken that "if a subjectively-well and objectively-robust individual has a slightly elevated blood pressure, then slightly elevated blood pressures must be normal." Even today this type of reasoning is prevalent. However,

14 Poulton, E. P., Symonds, C. P., and others. *Taylor's Practice of Medicine*, ed 15, Baltimore, William Wood & Company, 1936. Osler, W. *The Principles and Practice of Medicine*, ed 13, revised by H. A. Christian, New York, D. Appleton-Century Company Inc., 1938. Tice, F. *Practice of Medicine*, Hagerstown, Md., W. F. Prior Co., Inc., 1937. Cecil, R. L. *A Textbook of Medicine*, ed 4, Philadelphia, W. B. Saunders Company, 1937. Wetherby, M. Comparison of Blood Pressures in Men and Women, *Ann Int Med* 6:755, 1933. Mosenthal, H. O. The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis, in Christian, H. A. *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1929, vol 7, p 6.

15 Allen, E. V., in Musser, J. H. *Internal Medicine*, ed 3, Philadelphia, Lea & Febiger, 1938.

16 Hunter, A. Can Insurance Experiences Be Applied to Lengthen Life? *Proc A Life Insur Pres* 8:27, 1914.

a study over a period of years of many subjectively well and robust persons with slightly elevated pressures shows that they are not normal. This subject will be discussed in detail later.

3 All previous studies have included both normal and hypertensive pressures, these were averaged to arrive at a "normal" reading. It seems obvious that the abnormal blood pressures in the total population will distort the picture of the normal blood pressure averages. Some of the later workers spoke of this danger, but no author has ever attempted actually to separate normal from abnormal blood pressure groups in the statistical treatment of his series.

4 After the grossly hypertensive persons are excluded and there remains a sample of presumably normal persons, determination of the average—that most treacherous of statistical techniques—is by no means the best statistical measure. The modal pressure would state more accurately the most common blood pressure.

5 When blood pressure levels are read by physicians, especially in insurance examinations, there is a tendency for the physician to round out his figure to keep it within the acceptable levels set for that year. In our own experience with the six physicians who have taken most of the records used in this study, it was noticed that as soon as pressures as low as 100 mm were accepted as normal there was an increased incidence of these low readings, and when further revision reduced the lower limit of normal systolic blood pressure to 90 mm still lower readings were recorded. This is not an evidence of intellectual dishonesty, it means merely that few physicians will deny a person insurance because of a reading of 5 mm or so of mercury, nor in a routine periodic examination does a physician wish to excite the patient by the ominous words "low blood pressure" and the false pathologic implications they carry. He gives the patient the benefit of the doubt and so forever removes from statistical tables readings that are pertinent to the understanding of true normal blood pressure.

6 Another source of error noted by practically all workers is the tendency on the part of physicians to round out their manometer readings to the nearest unit of 10.

7 The "normal" is sometimes defined as the "most common", however, even the most common blood pressure need not be a normal blood pressure, for purely statistical interpretation does not necessarily reveal true physiologic levels. To understand the real meaning of vascular tension one must augment statistical data with life histories of blood pressure and with mortality data.

8 Even after all these statistical and clinical precautions are taken, one is not justified in assuming that the range of blood pressure so obtained is the true normal physiologic measure for the human being.

It must be remembered that the studies are, in the main, studies of confined, sedentary persons with faulty hygienic habits. One must interpret such studies in terms of "normal" living.

The interplay of all these errors, especially the inclusion of the abnormally high readings of hypertensive persons in values for the total groups studied, has resulted in blood pressure levels that are obviously too high. Many clinicians with even a limited experience question these levels, and this has had its effect on studies of blood pressure in the last two decades. A chronologic study of the outstanding contributions on blood pressure proves this¹⁷. In the last quarter of a century the level of normal pressures has been persistently lowered. This shift of levels was apparent twenty-five years ago and was recognized by Janeway^{3e}. Fifteen years ago it was mentioned by Alvarez^{3f}. In the recent literature occasional statements have appeared which fix normal blood pressure at levels which in 1910 would have been considered to indicate hypotension. Is this declining standard due to a drop in the blood pressure of normal persons, or are ideas concerning normal levels changing? The collected data of various authors on blood pressure measurements show the latter to be true, though the change in ideas is, to be sure, very slow. Through years of application, the old formula "100 plus your age" has become a deeply rooted conception, so much so that even otherwise competent statistical research has been colored by this established idea.

17 (a) Woley, H. P. The Normal Variation of the Systolic Blood-Pressure. A Study of One Thousand Cases, *J. A. M. A.* **55** 121 (July 9) 1910. (b) Norris, G. W. Blood Pressure, Philadelphia, Lea & Febiger, 1916. (c) Osborne, O. T. Disturbances of the Heart, ed. 3, Chicago, American Medical Association Press, 1925. (d) Granger, A. S. Present Conception of Essential Hypertension *J. A. M. A.* **93** 819 (Sept. 14) 1929. (e) Alvarez, W. C., and Stanley, L. L. Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards. Statistical Analysis, *Arch. Int. Med.* **46** 17 (July) 1930. (f) Fishberg, A. M. Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934. (g) Huber, E. G. Systolic and Diastolic Blood Pressure in Healthy Men, *Human Biol.* **5** 542, 1933. (h) Wright, S. Applied Physiology, London, Oxford University Press, 1934. (i) Mosenthal, H. O. Normal Blood Pressure, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1931, vol. 12, p. 644. (j) Dingman, H. W. Selection of Risks for Life Insurance, Health Insurance, Accident Insurance, Cincinnati, National Underwriter Co., 1935. (k) Corwin, J., and Herrick, W. W. Relation of Hypertensive Toxemia of Pregnancy to Chronic Cardiovascular Disease, *J. A. M. A.* **88** 457 (Feb. 12) 1927. (l) MacKenzie, L. F., and Wells, P. V. On The Interpretation of Blood Pressure, *Proc. A. Life Insur. M. Dir. America* **19** 89, 1932, New York, Press of Recording and Statistical Corporation, 1933. (m) Wiggers, C. J. Physiology in Health and Disease, Philadelphia, Lea & Febiger, 1934. (n) Dally, J. F. H. High Blood Pressure, in Rolleston, H. The British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1936, vol. 2, p. 503. (o) Palmer, J. H. Blood Pressure in the Years Following Recovery from Coronary Thrombosis, *Lancet* **1** 735, 1937.

Finally, no previous study has incorporated the continuous records of blood pressure over long spans of time, nor have conclusions been checked with mortality data. These two additional phases of analysis are indispensable to an intelligent understanding of the subject. They add a dynamic interpretation to what has been thus far merely a static study.

STATISTICAL ANALYSIS OF THE TOTAL GROUP

To arrive at a better solution of the problem of the range of normal blood pressure we undertook an exhaustive statistical study of 7,478 men and 3,405 women selected at random. All lived in or around Chicago and were of that economic class which can afford an insurance policy of \$1,000 or more. The majority came for a routine periodic examination given gratis by their insurance company. Most of the examinees had either no complaints or minor ones.

In selection of any source material for a study of normal blood pressure the sample should be truly representative of the total population in respect to all variables (age, sex, height, weight and occupation). Given a representative sample, the physical examination must also be rigidly standardized. Most samples hitherto studied have not met one or another of these requirements. Generally, insurance statistics have represented examinations made under a variety of conditions¹⁸. Other studies have been made on select groups of army men, prisoners or students. Some have even included patients in hospitals.

Our group, while based on accepted risks for life insurance companies, represents for the most part persons examined long after the original policy examination and, according to Dublin,¹⁹ of the Metropolitan Life Insurance Company, is therefore more generally in accordance with a random sample of the population. In general, then, our group comes close to being a typical portion of all age groups between 20 and 70, includes both sexes and was taken under conditions of general health comparable to those of any random group in the total population. It must be remembered, however that the group was composed for the most part of urban men and women who were relatively sedentary in their occupation and recreation.²⁰

18 Wright and his associates presented an illuminating description of the force of possible error in blood pressure readings by different physicians (Wright, I. S., Schneider, R. F., and Ungerleider, H. E. Factors of Error in Blood Pressure Readings. Survey of Methods of Teaching and Interpretation, *Am Heart J* **16** 469, 1938). See also Diehl, H. S., and Lees, H. D. The Variability of Blood Pressure. Study of Systolic Pressure at Five Minute Intervals, *Arch Int Med* **44** 229 (Aug.) 1929.

19 Personal communication to the authors, Feb 9, 1937.

20 The thirty minute examinations of the persons included in our study were standardized as far as possible. All blood pressure readings were taken with the

For 7,478 men the arithmetic average, or mean systolic blood pressure was found to be 121 mm. About two thirds of the men had blood pressures within a range of 17 mm of the average (designated as the standard deviation of the mean). Generally, then, the blood pressure of men ranged from 104 to 138 mm. In a similar sample of 3,405 women the average systolic pressure was 117 ± 10.8 mm. Hence, the systolic pressure of most women ranged from 106 to 128 mm. The average diastolic pressure for men was 74.4 mm, with a standard deviation of 10.5 mm. The average diastolic pressure for women was 71 ± 11.5 mm. For the most part, then, diastolic pressure for men ranged from 64 to 85 mm, and for women, from 60 to 83 mm.

If one works only with a broad, unselected sample, it is better to determine where the values congregate than to use averages. To state it in statistical terms: What is the modal pressure of these groups? Most of the values for men were congregated around 115 mm systolic and 71 mm diastolic (table 1), and those for women were most frequently grouped around 113 mm systolic and 70 mm diastolic. We consider these modal pressures more significant than the mean or average readings which are so generally cited.

Almost two thirds of all blood pressures were below 125 systolic and 80 diastolic. This is a more important statement than the modal or average figure, because, as we shall show, the lower levels are highly desirable. Comparison of the mean and the modal systolic pressure indicates strongly that the abnormally high pressures effect a considerable distortion of the average figure, the "average" therefore, cannot rightly be interpreted as "normal" (chart 1). Because this distortion falls principally in the upper age groups, the false impression prevails

subject sitting and on the left arm with a mercury manometer. A total of six physicians made all of the examinations abstracted in the 10,883 cases of our total group study. Most of the women were examined by a woman physician. Each physician was acquainted with the technic of the others, and in instances of interestingly high or low readings the physicians checked each other's work. In all cases of abnormally high or low readings a reading was repeated as a check at the end of the examination to discount emotional or transitory rises, the lowest readings being recorded. In some cases three or more readings were necessary. The auscultatory method, with Bowles's bell diaphragm stethoscope, was used throughout, though occasionally the tactile method was used as a check.

The diastolic reading was made at the commonly accepted fourth phase—at the end of the loudest sound. If the rate of deflation is too rapid the reading may be distorted, and usually the examiner catches the reading too high. Deflation should be rather slow. A value of 0 diastolic should never be recorded, however, when the diastolic sound is faint and difficult to read or when some sounds continue to be audible down to or near zero, the flat diaphragm of the stethoscope should be inserted under the lower edge of the cuff, along the course of the brachial artery, on the medial aspect of the lower third of the upper part of the arm. This usually clarifies the diastolic sounds, as well as the systolic

TABLE 1—Relation of Age to Blood Pressure in 7,478 Males and 3,405 Females (Total Group)

	Under 15	Age Groups													80 and Over	All Ages
		15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79		
Men																
Number of cases	17	96	539	1,113	1,202	1,185	1,064	903	550	303	227	116	48	16	9	7,478
Percentage of total	0.2	1.3	7.2	14.9	16.1	15.8	14.2	12.1	7.4	5.3	3.0	1.6	0.6	0.2	0.1	100.0
Systolic pressure, mm																
Mean	98.7	118.3	119.0	118.5	117.5	117.6	120.1	122.7	125.6	129.6	131.7	138.6	137.2	151.4	117.5	121.0
Modal	92.5	123.4	120.8	117.3	113.6	112.5	118.3	114.9	113.0	123.3	122.2	124.2	130.6	126.2	110.0	115.9
Percentage under 100	64.7	5.2	4.6	5.0	5.2	5.7	6.3	5.0	1.7	1.8	1.0	2.6	4.2			5.3
Percentage under 120	94.1	50.0	51.0	53.0	58.6	50.2	51.1	49.6	41.3	37.4	31.2	23.3	29.2	18.8	11.1	51.3
Percentage over 140		3.1	5.6	4.8	1.6	5.1	9.2	1.5	2.2	23.4	29.1	43.9	43.8	62.5	55.6	10.8
Diastolic pressure, mm																
Mean	56.0	68.2	70.8	72.0	72.7	74.0	75.7	77.0	77.3	78.2	77.5	76.7	77.3	80.0	87.5	74.4
Modal	50.6	67.0	72.3	72.0	71.8	71.6	71.5	70.7	70.4	72.5	69.4	69.5	69.5	85.1	72.5	71.4
Percentage under 60	64.7	1.1	7.8	6.5	5.1	3.8	3.1	3.4	3.5	2.3	1.0	7.0	4.2	12.5		1.8
Percentage under 80	100.0	91.0	82.9	79.7	79.8	73.3	65.5	61.1	60.2	59.0	60.3	63.8	60.1	43.8	41.4	66.6
Percentage over 90		1.0	2.0	3.1	3.4	5.0	8.0	11.9	12.8	13.9	11.1	16.4	12.5	37.5	11.1	7.3
Women																
Number of cases	12	80	302	531	609	569	495	349	201	141	71	35	8	2		3,405
Percentage of total	0.4	2.4	8.9	15.6	17.9	16.7	14.5	10.2	5.9	4.1	2.1	1.0	0.2	0.1		100.0
Systolic pressure, mm																
Mean	106.7	107.4	108.4	110.2	111.6	114.4	119.0	125.4	125.8	138.2	142.8	145.9	136.9	167.5		117.0
Modal	101.6	109.8	106.6	110.5	111.3	112.2	112.7	114.9	112.3	116.1	126.0	139.6				113.4
Percentage under 100	33.3	21.3	22.8	22.1	19.8	15.5	14.7	8.3	7.0	5.0	5.6	2.9	12.5			15.8
Percentage under 120	83.3	88.9	84.1	79.2	80.3	69.2	58.2	45.6	46.8	34.0	21.1	20.0	25.0			65.1
Percentage over 140				1.5	1.8	5.4	12.3	20.9	21.4	37.6	46.5	57.2	71.4	50.0		10.0
Diastolic pressure, mm																
Mean	64.2	63.9	65.4	67.1	69.0	70.7	73.2	75.4	75.7	79.0	81.0	80.2	75.0	80.0		71.0
Modal	55.5	61.5	62.7	64.1	67.5	70.7	71.1	70.6	70.6	76.0	82.5	81.4				70.1
Percentage under 60	11.7	31.3	25.2	21.5	17.4	14.4	11.5	7.2	5.5	7.1	5.6	5.7				14.7
Percentage under 80	83.3	95.0	95.0	90.0	83.3	82.4	71.3	65.3	66.2	56.0	43.7	48.6	75.0	50.0		78.6
Percentage over 90				0.9	3.0	5.1	9.1	11.5	10.9	19.9	22.5	20.0	12.5	50.0		6.3

that "normal" blood pressure rises with age. The coefficient of correlation of age and systolic pressure for the total group was 0.14 ± 0.01 for men and 0.41 ± 0.01 for women, that of age and diastolic pressure was 0.22 ± 0.01 for men and 0.35 ± 0.01 for women. Neither of the correlations for men is significant of a rise in blood pressure with age. The slight significance of the correlation for women will be discussed later.

Since our total group of 10,883 persons, like every other group previously analyzed, contains this conglomerate of normal and hypertensive persons, it is not justifiable to draw conclusions concerning normal levels of blood pressure from such a sample. One must devise some method of roughly separating the pathologic from the normal pressures before the group is subjected to an extensive statistical

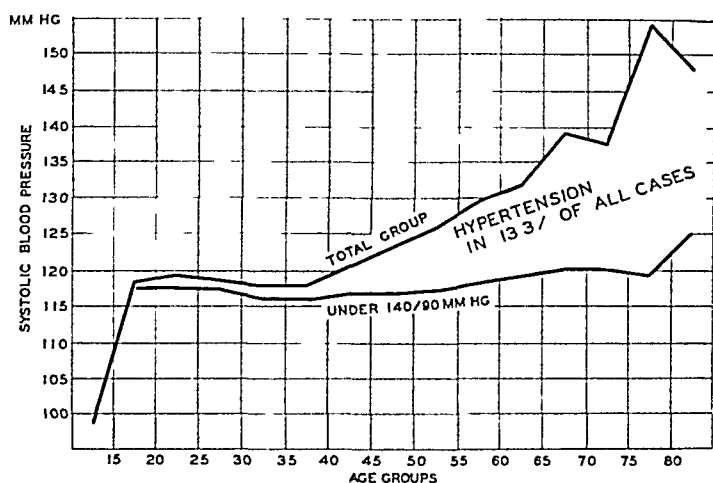


Chart 1—Effect of hypertension on the blood pressure curve. The average systolic pressure of the total group of 7,478 men rises with age, however, when the obviously hypertensive persons (over 140 systolic and 90 diastolic) are excluded, the average blood pressure of the 6,485 men with blood pressures below this level does not rise with age.

analysis. This we shall do in the next section of the paper. We cannot yet say, therefore, what "normal" blood pressure should be from this statistical study of our total group of 10,883 persons.

DELIMITED GROUP

(Pressure of 140/90 and Over Excluded)

Study of the distribution of presumably normal blood pressures necessitates drawing an arbitrary line between normal blood pressure and hypertension at a point which is compatible with accepted opinion and at the same time overcomes the inherent errors of the total group study. There is accumulating a large body of evidence, such as statistical

and clinical studies and mortality rates, that demand the recognition of a level of 140 mm systolic and 90 mm diastolic at least (as will be shown even this is much too high) beyond which the pressures are definitely hypertensive. During the last ten years an ever increasing number of authorities in this field have placed 140 mm as the upper limit of normal systolic pressure. Allen¹⁵ stated "A systolic pressure of more than 140 mm should be regarded as abnormal." Alvarez^{17c} stated "A pressure of 140 mm is just as abnormal in an old man as in a young one." Hubei^{17g} stated "A systolic pressure of 140 mm or more is regarded as above normal." Faught²¹ stated "A pressure above 140 mm is unsafe at any age." Diehl and Sutherland²² also used 140 mm as the upper limit of normal, as have many others. Mortality studies have shown conclusively that pressures above 140 mm are definitely associated with a sharp increase in mortality.²³ For the purposes of this study we have, arbitrarily to be sure, used a pressure of 140 mm as the dividing line above which an abnormal systolic blood pressure definitely exists.²⁴

There seems recently to be an equal consensus that the upper limit of normal diastolic blood pressure should be placed at 90 mm. (In our own selection 93 per cent of the readings were below 90 mm.) It seems apparent that a higher level is in complete discord with any rational view of diastolic pressure. We have arbitrarily chosen 90 mm, therefore as the upper normal diastolic pressure for the selection of our delimited group. The delimited group contains only those persons whose blood pressure was under 140 mm systolic and 90 mm diastolic.

There are other reasons for selecting this group for detailed analysis. In order to orientate ourselves as to which range of blood pressures effected most of the distortion of the mean in the total group, we serially discarded the upper brackets of the higher pressures and noted the effect on the age-blood pressure curve. The rise with age that is

21 Faught, F. A. Simple Method for Determining Normal Average Systolic Blood Pressure at Any Age, *M. J. & Rec.* **135** 160, 1932.

22 Diehl, H. S., and Sutherland, K. H. Systolic Blood Pressure of Young Men, *Arch. Int. Med.* **36** 151 (Aug.) 1925.

23 (a) Fisher, J. W. Mortality Statistics, Milwaukee, The Northwestern Mutual Life Insurance Company, 1935. (b) Report of the Joint Committee on Mortality of the Association of Life Insurance Medical Directors and the Actuarial Society of America, New York, 1925.

24 We have not discarded any of our extremely low blood pressure readings, for two reasons. First, in our sample less than 1 per cent of the readings for men and 18 per cent of those for women were below 90—an incidence which would not materially change our final results. Second, the dividing line between low and normal pressure has decreased steadily since the invention of the sphygmomanometer. Norris,^{17b} in 1916, gave 115 mm, and Granger^{17d} and others, fifteen years later, used 90 mm, as the lowest normal systolic blood pressure.

seen in the total group became proportionately less conspicuous as the upper levels were discarded. At the level of 140 mm a significant difference from the previous distribution was noted. The mean level of blood pressure was nearly constant at all ages (chart 1). The mean blood pressure does not rise with age. The same type of serial elimination was carried out for the diastolic pressures, and the same tendency was apparent at the 90 mm level.

The exclusion of pressures over 140 systolic and 90 diastolic does not alter the conclusions of the analysis. The results in our series would have been substantially the same had the level of delimitation been placed at 150 systolic and 95 diastolic. In addition, the modal pressure of the total group with its standard deviation—a more accurate measure of normal range—extends from 106 to 126 mm of systolic pressure, which is essentially what is found in the delimited group. The technic of delimitation is only one of several methods which we have used to establish a normal range. The modal pressure of the total group, the continuous records of blood pressure and the study of mortality at different levels of pressure are all essential in establishing a true normal range.

Composition of Delimited Group (9,473 Persons)—When the persons with gross hypertension (temporarily and arbitrarily set at 140 systolic and 90 diastolic and over) were excluded from the total group, 13.3 per cent of the men and 11.5 per cent of the women were discarded because of obviously high pressure, leaving 6,458 men and 3,015 women within the delimited range. A statistical study of such a group should come closer to determination of normal levels than a study of the original sample.

Age Distribution—The mean age of the men was 38.3 ± 0.14 . The women were generally two years younger, with a mean age of 36.1 ± 0.19 . The median age for the men was 37.1, showing a skewness of 0.32 to the left. From this it is apparent that the older age groups caused a slightly greater distortion of the mean than did the younger age groups, hence we did not have a perfect chance distribution. The median age for the women was 35.1, with a skewness of 0.29. This shows about the same distortion of the mean as the value for men, both figures showing a slightly significant distortion, in which case the modal age, 34.7 for men and 33.1 for women better shows the most intense concentration of the person in this sample of the population. As the standard deviation of the mean for men was 11.09 and that for women was slightly less, being 10.26, the distribution of the subjects around the points of central tendency shows that two-thirds were between the ages of 27 and 49 years and 95 per cent were between the ages of 17 and 61.

Distribution of Systolic Blood Pressures—When the extreme end of an array is discarded, as we have done by eliminating cases of gross hypertension, the mean or arithmetic average will automatically decrease, but in a good distribution the mode should not change. This holds true for our sample. While the mean pressure for the total group of men was 121 ± 0.20 mm, the mean for the limited group was 116.3 ± 0.14 mm, the mode for the total group of men was 115.9 mm, and the mode for the limited group was nearly identical, 115.1 mm. A standard deviation (two thirds of the distribution around the mean) of 10.92 mm in the limited group shows that the systolic blood pressures of men (table 2) seemed to center around 105 to 127 mm (116 ± 10.91 mm).

This follows nicely in the array for women (table 3). The distortion of the mean in the total group caused a corresponding slight distortion of the mode, and while the expected fall of the mean occurs—from 117 to 111.6 mm—the mode shows only a fall from 113.9 mm, in the total group, to 111.6 mm, in the delimited group. Because the mean and the median approximate each other in the limited group, 111.6 mm seems more reliable. With a standard deviation of 12.3 mm, it seems safe to conclude that the systolic blood pressures of this group of women, regardless of age, ranged from 100 to 125 mm²⁵.

To state this in simpler and more exact terms, the percentage groupings of the distribution were as follows:

6,458 Men	3,015 Women
86% between 90 and 130 mm systolic	89% between 90 and 130 mm systolic
54% between 100 and 120 mm systolic	56% between 100 and 120 mm systolic
6% below 100 mm systolic	18% below 100 mm systolic
25% below 110 mm systolic	44% below 110 mm systolic

When one considers that 44 per cent of the women and 25 per cent of the men had a systolic blood pressure below 110 mm, whereas the percentage with a pressure over 140 mm was about the same for men and women, it is seen that women are more likely to have extremely low pressures than are men. However, this must be qualified by noting that women with low blood pressures were in the younger age groups.

A study of the correlation of systolic blood pressure with age is more informative. In the delimited group of men (chart 2) the distribution of low blood pressures did not show a significant change at any

²⁵ If all of the men were lined up in the serial order of ascending systolic blood pressure the middle man of the group would have a pressure of 115.9 mm. The skewness of the distribution for men was 0.11, the distribution for women had no skewness and the median was the same as the mean, 111.6 mm. The greater coefficient of variation for women than for men is due to a fundamental difference between the distributions for men and for women when age is taken into consideration.

TABLE 2—*Relation of Age to Blood Pressure in the Delimited Group (Pressures Over 140/90 mm Excluded)*

	Age Groups															Per centage of Total Number
	Under 15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80 and Over	
Systolic pressure, mm																
Under 50	3				7	4	7	5	6	1	2					42
90-99	8	5	22	52	56	63	60	40	20	18	7	3	2			356
100-109	2	10	83	192	230	233	174	155	75	50	23	8	2	2		55
110-119	3	33	167	351	411	392	300	247	143	77	39	16	10	1	1	1,239
120-129	1	35	159	295	297	289	259	194	109	85	53	22	6	1	1	2,191
130-139		9	69	146	124	111	129	91	65	51	30	15	7	2	2	340
Total	17	92	503	1,040	1,125	1,092	929	732	418	282	154	64	27	6	4	1,806
Percentage of total	0.3	1.4	7.7	16.0	17.4	16.9	14.3	11.3	6.5	4.4	2.4	1.0	0.4	0.1	0.1	100.0
Mean	98.7	117.4	117.3	116.8	115.7	115.4	116.3	115.8	116.6	117.6	118.6	119.9	119.9	119.2	125.0	116.3
Standard deviation	12.08	10.15	10.58	10.72	10.58	10.19	11.18	10.95	11.18	11.66	11.62	11.69	11.40	11.40	125.0	10.92
Standard error	2.93	1.06	0.47	0.33	0.32	0.32	0.55	0.40	0.55	0.69	0.91	1.39	2.19	2.19	2.19	0.14
Mode	92.5	122.5	119.7	115.9	113.3	113.0	116.9	111.9	116.0	121.5	124.9	124.7	120.2	120.2	124.9	115.1
Percentage under 100	64.7	3.4	5.0	5.1	5.6	6.2	7.2	6.2	6.2	6.7	5.8	4.7	7.4	7.4	6.7	6.7
Percentage under 110	76.4	16.3	21.5	23.9	26.1	27.5	25.9	27.4	24.2	24.4	20.7	17.2	14.8	33.3	25.3	25.3
Percentage under 120	94.1	52.2	54.7	57.7	62.7	63.4	58.2	61.1	58.4	51.7	46.0	42.2	51.8	50.0	25.0	59.2
Percentage under 130	100.0	90.3	86.4	86.1	89.1	89.8	86.1	87.7	84.4	81.9	80.4	76.6	74.0	66.7	50.0	86.9
Diastolic pressure, mm																
Under 60	11	11	41	71	61	45	32	30	18	9	9		2	2		347
60-69	3	43	184	337	335	297	231	190	101	66	48	24	6	2		1,867
70-79	3	30	203	159	546	512	429	325	191	139	66	26	16	1	4	2,950
80-89		8	75	173	183	238	237	187	108	68	31	9	3	1		1,321
Total	17	92	503	1,040	1,125	1,082	929	732	418	282	154	64	27	6	4	6,485
Percentage of total	0.3	1.4	7.7	16.0	17.4	16.9	14.3	11.3	6.5	4.4	2.4	1.0	0.4	0.1	0.1	100.0
Mean	56.0	68.0	70.2	71.1	71.6	72.6	73.4	73.3	73.4	73.3	71.9	69.9	71.2	66.7	72.5	72.1
Standard deviation	9.80	7.68	8.37	7.87	7.62	7.81	7.75	8.06	7.81	7.62	8.06	8.12	6.48	7.97	72.5	7.97
Standard error	2.38	0.80	0.37	0.24	0.23	0.21	0.38	0.30	0.38	0.45	0.65	1.02	1.25	0.10	0.10	0.10
Mode	50.6	67.7	72.3	72.9	73.1	72.9	73.4	73.0	72.5	73.0	72.2	72.6	73.0	73.0	73.0	73.0
Percentage under 60	64.7	12.0	8.2	6.8	5.5	4.2	3.5	4.2	1.3	3.2	5.8	7.7	7.1	33.3	5.4	5.4
Percentage under 70	82.3	58.8	14.8	39.2	35.3	31.4	28.3	30.2	28.5	26.6	36.9	45.2	29.6	66.7	34.2	34.2
Percentage under 80	100.0	91.4	85.2	83.3	83.8	78.3	74.5	71.6	74.2	75.9	79.7	85.7	88.9	83.4	100.0	79.8

TABLE 3—Relation of Age to Blood Pressure in 3,015 Women in the Delimited Group (Pressures Over 140/90 mm Excluded)

Systolic pressure, mm	Age Groups														Per cent of Total	
	All Ages															
	Under 15	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79		80 and Over
Under 90	4	3	7	15	16	6	7	1	14	7	1	3	1	1	56	19
90-99	2	14	62	102	97	82	66	28	36	15	7	3	1	3	181	160
100-109	4	27	100	141	156	148	92	58	44	26	7	3	3	1	783	200
110-119	2	27	85	161	186	157	123	72	44	26	7	3	3	3	895	296
120-129	2	6	36	73	101	97	83	60	40	22	12	3	3	3	535	177
130-139		2	11	30	30	34	53	48	23	16	11	5	1	1	263	88
Total	12	79	301	522	586	524	424	261	157	86	38	15	3	1	3,015	1000
Percentage of total	0.4	2.6	10.0	17.3	19.4	17.4	14.1	8.9	5.2	2.9	1.3	0.5	0.1	0.03	100.0	
Mean	106.7	107.2	108.3	109.4	110.4	111.4	113.1	115.9	116.0	117.7	119.9	119.8	109.2	132.5	111.6	
Standard deviation	10.95	10.25	11.05	11.96	11.70	11.62	12.88	12.57	11.75	12.12	13.56	13.53	109.2	132.5	122.7	
Standard error	3.16	1.15	0.64	0.52	0.48	0.51	0.63	0.77	0.94	1.31	2.20	3.50			0.22	
Mode	101.6	110.2	106.8	111.5	112.5	111.1	112.5	112.9	113.9	115.9	126.1				111.6	
Percentage under 100	33.3	21.7	22.9	22.4	19.3	16.8	17.2	10.9	8.9	8.1	10.5	6.7	33.3		17.8	
Percentage under 110	50.0	55.9	56.3	49.6	47.9	45.0	38.9	32.6	31.8	25.6	21.0	26.6	66.6		43.8	
Percentage under 120	83.3	90.1	84.5	80.5	77.7	75.0	67.9	59.6	59.8	55.8	39.5	46.7	66.6		73.5	
Percentage under 130	100.0	97.7	96.5	91.4	91.9	93.5	87.1	82.1	85.3	81.1	71.1	66.7	66.6		91.2	
Diastolic pressure, mm																
Under 60	5	25	76	114	106	65	57	25	11	10	4	2			500	166
60-69	1	37	123	199	222	193	131	80	44	26	10	3	2	1	1,073	356
70-79	1	18	88	163	179	203	150	108	69	44	12	7	1		1,042	316
80-89	2	3	14	46	79	61	77	54	33	16	12	3			100	113
Total	12	79	301	522	586	524	424	267	157	86	38	15	3	1	3,015	1000
Percentage of total	0.4	2.6	10.0	17.3	19.4	17.4	14.1	8.9	5.2	2.9	1.3	0.5	0.1	0.03	100.0	
Mean	61.2	63.5	65.3	66.7	68.0	69.0	70.1	71.2	71.7	70.9	72.9	71.2	67.5	67.5	68.5	
Standard deviation	9.43	8.17	7.81	8.71	9.17	8.09	8.05	8.57	8.24	8.71	9.83	8.06			8.85	
Standard error	2.73	0.92	0.45	0.38	0.38	0.35	0.18	0.32	0.66	0.94	1.60	2.08			0.16	
Mode	55.5	62.3	62.9	63.7	67.1	72.3	72.8	73.0	73.5	73.3	76.8	72.5			70.3	
Percentage under 60	41.6	31.7	25.3	21.8	18.1	12.4	13.4	9.4	7.0	11.6	10.6	13.3			16.6	
Percentage under 70	71.9	73.5	66.2	60.0	56.1	49.6	44.2	39.3	35.1	41.9	36.9	33.3	66.6	100.0	52.2	
Percentage under 80	83.2	96.3	95.4	91.3	86.6	88.3	81.7	79.7	79.1	81.4	68.5	80.0	100.0	100.0	86.8	

age²⁶ As many 55 year old as 20 year old men had blood pressures under 100 mm. The same held true for pressures under 110 mm. The number with pressures over 120 mm showed a slight increase with age. Up to the age of 60, one half or more of the men of all ages in the limited group had a systolic blood pressure lower than 120 mm. There was an increase in incidence of pressures over 130 mm with increase in age. Apparently (table 2), most men who have low pressures (under 110 mm) do not show any rise in systolic pressure throughout their lives, and about a tenth of the men with pressures under 120 mm may show a slight rise in pressure after the fiftieth year. Finally the systolic pressures of about half the men of any age in this limited group did not rise above 120 mm, and that of about three-quarters never rose above 130 mm.

Because most of the variation in pressures occurs at levels over 120 mm, our data so far seem to indicate that the hypertensive men are

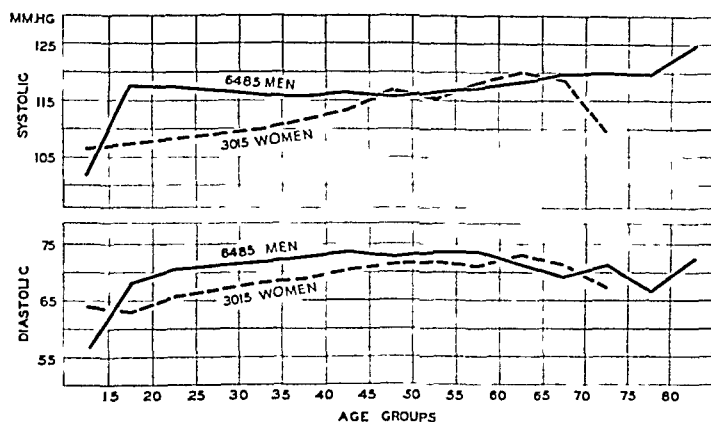


Chart 2—Effect of age on blood pressure. After the obviously hypertensive persons are excluded, the limited group of men, with pressures under 140 systolic and 90 diastolic, shows little tendency toward a rise in blood pressure with age. The blood pressure of women is lower than that of men in the younger age groups.

those who have had systolic pressures above 120 mm at an early age. In other words, men with moderately high systolic pressures (120 to 140 mm) at any age, but especially in the younger group, are probably the ones who will have hypertension years later.²⁷

The age distribution of systolic pressures for women shows one striking difference from that for men. While women over 40 years of age have about the same blood pressure as do men, younger women have substantially lower pressures. The mean systolic pressure of women under 40 years of age was 110.4 mm, that of men was 117 mm.

²⁶ The coefficient of correlation of age with systolic pressure for men in the limited group was 0.02 ± 0.01 , for women it was 0.22 ± 0.01 .

²⁷ A study of our ten year continuous records will confirm this.

After the age of 40 the mean pressure was about 118 mm for both men and women. The change in women is not sudden but is a steady climb in mean pressure, starting just after the age of 20 and continuing into old age. To emphasize these low pressures in young women, we note that about 50 per cent had pressures under 110 mm and more than 20 per cent had pressures under 100 mm (table 4).

While there was an incidence of 2 per cent of readings under 90 mm for the young women, only a few low readings were found for women after the age of 40. In men the incidence of readings under 90 mm was greater in the old than in the young. It is interesting to note, however, that there were twice as many women as men whose systolic pressure was under 100 mm and as many women whose systolic pressure was under 90 mm, even in the older age groups. Almost 80 per cent of the young women showed systolic pressures under 120 mm, and the systolic pressures of more than 60 per cent of the older women were

TABLE 4—*Distribution of Blood Pressure in Men and Women*

Blood Pressure, Mm	Men		Women	
	Under 40 Years of Age, %	40 Years of Age and Over, %	Under 40 Years of Age, %	40 Years of Age and Over, %
Under 90	0.5	0.8	2.3	0.9
Under 100	5.9	6.5	20.2	13.0
Under 110	25.2	25.2	48.6	34.1
Between 110 and 120	35.1	31.9	30.6	27.8
Over 120	39.7	42.9	20.9	38.1
Over 130	11.9	15.0	5.3	15.9
Number of cases	3,869	2,616	2,024	991

under 120 mm. In men the difference between young and old was less marked. We have seen that the percentage of women with systolic pressures over 110, 120 and 130 mm increases with age.

From this distribution it is apparent that most women have low blood pressures up to the age of 40 and that the pressures will be slightly higher after 40, but are lower than at the corresponding ages in men. The systolic pressure of about one half of the population never greatly exceeds 120 mm. A rise in pressure in women is deceptive unless it is realized that women start with pressures far below those of the men. The modal pressure of women is lower than that of men even in the older age groups. Almost half the younger women have pressures under 110 mm. Younger women generally have systolic pressures up to 15 mm lower than those of young men, and older women have pressures equal to or less than those of older men. It must be remembered that we are not concerned with hypertensive women when we say this.

Distribution of Diastolic Blood Pressures—The mean diastolic pressure for men was 72.1 mm, with a modal pressure of 73 mm. The

women had a mean pressure of 68.5 mm and a modal pressure of 70.3 mm. The standard deviation for men was 7.9 mm and that for women was 8.8 mm. Thus, the men usually had diastolic pressures between 64 and 80 mm, while for women the values were slightly lower, between 60 and 77 mm (tables 2 and 3).

When this distribution is analyzed from the standpoint of specific age groups, the very low pressures in men are seen to occur chiefly in youths under 20 years of age, hence the mean shows a slight rise which after the age of 20 is not significant. We cannot, therefore, find a normal rise of diastolic pressure in normal persons.²⁸ A further corroboration of this is seen in the more pertinent fact that the modal pressure hovers around 72 to 74 mm at all ages. However, the number of low diastolic pressures (under 70 mm) decreases up to the age of 55 years, but after the age of 55 the number under 70 mm returns to its earlier incidence. We have not adequately accounted for this variation. The percentage of diastolic pressures between 70 and 80 mm remains constant throughout life. The percentage over 80 mm increases in late middle age. Apparently this is the pressure which favors hypertension.

The diastolic blood pressure of women, like the systolic, varied slightly with age. The levels for older women were about the same as those for men, but the younger women (up to 30 years of age) usually had diastolic pressures at the lower 60 mm level. As in the case of systolic pressure, the diastolic pressure of older women was not, on the whole, greater than that of men of corresponding age, but that of the younger women started at a much lower value.

It seems from the foregoing data that the diastolic pressure should normally be below 80 mm. It is hard to imagine why 90 mm was ever chosen as the upper limit of normal. Even in the total group, with hypertensive persons included, we were able to establish the statistical fact that the greater number of persons had pressures below 80 mm. Because the diastolic fluctuation was less marked than the systolic and because the measurements with a central tendency were all in the low 70 mm class, it seems from a purely statistical analysis that normal diastolic pressure should be 80 mm or below. Alvarez,^{17e} Saller²⁹

This study of a delimited group of persons bears out our conclusions in the study of the modes of the total groups, that is, a great number of persons do not show a rise in blood pressure,³⁰ for in our delimited group at least half the older persons had systolic blood pressures below 120

28 The coefficient of correlation of age with diastolic pressure for men was 0.09 ± 0.01 , for women it was 0.22 ± 0.1 .

29 Saller, K. Blood Pressure Changes Due to Age, *Ztschr f d ges exper Med* 58:683, 1927.

30 MacWilliam, J. A. Blood Pressure in Man Under Normal and Pathologic Conditions, *Physiol Rev* 5:303, 1925.

mm. It is apparent that most men in this group had pressures around the 116 ± 10 mm level at any age. Older women had pressures similar to those of men, but younger women had pressures much lower than men. The pressures which were most frequent for women were around 112 ± 10 mm. Furthermore, it seems from this study that hypertension occurs in persons who earlier in life have shown systolic pressures above 120 mm.

The diastolic levels appear to be in the low 70 mm class most frequently for both men and women, although for young women they generally are lower. At any rate pressures between 60 and 80 mm comprise the majority for both men and women. Pressures of 80 mm and over should, in the light of this study, be classified as indicating hypertension.

Summary—Many recent authorities agree that the upper level of normal blood pressure lies around 140 systolic and 90 diastolic. We have discarded all subjects with pressures above this level, a delimited group remaining in which the normal blood pressure of both men and women probably lies under 127 mm systolic and 80 mm diastolic. We have further demonstrated that the majority of persons do not show a rise of blood pressure with age. As many old men as young men have low blood pressures. We have still not explained the fact that the 10 per cent of the population which shows a rise in pressure had at an earlier age pressures which were apparently normal. It would be interesting to find out what those blood pressure levels were. Our study of static pressures shows that the major shift in incidence with increasing age falls within the groups showing pressures of over 120 systolic and 80 diastolic.

This is as far as any static study of pressure can take us. Although a static study shows clearly the major trends of blood pressure and the approximate levels at different ages, it does not take into account the daily and yearly variations in blood pressure. This continuously changing physiologic process can be measured only through a study of continuous records. The life history of blood pressure as a dynamic process is the topic of the next section.

CONTINUOUS BLOOD PRESSURE STUDIES

Ever since blood pressure became important as a diagnostic aid, workers in the field have bemoaned the fact that their material did not include studies of continuous blood pressure records over long periods. In a rather extensive review of the literature we have found only one or two studies that approach the problem from the standpoint of yearly blood pressure levels for presumably normal persons over a period of years. For our study of the continuous blood pressure of 500 apparently well men, each record contained the abstract of an annual physical

examination over a period of about ten years³¹ These records were taken under the same standardized conditions as were those of the previous group of 10,883 persons The study endeavored to embrace all adult age groups and all levels of blood pressure

1 The first characteristic that strikes one in even a casual perusal of yearly continuous records is the marked variation that every person's blood pressure shows This yearly variation merely reflects the daily physiologic rhythm of blood pressure The pattern of this variation is much like that of temperature It is lowest in the early morning, during sleep and highest in the late afternoon Other factors, such as emotion and exercise, superimpose additional flux on the diurnal flow of pressure

TABLE 5—*Average Range of Differences Between Highest and Lowest Readings*

Number of Men	Systolic Pressure Level Always Over	Difference, Mm
5	140 mm	36
9	130 mm	24
23	120 mm	23
53	110 mm	18
58	100 mm	19

TABLE 6—*Yearly Variation in Blood Pressure*

Systolic Pressure, Mm	Number of Men	Average Mean Yearly Variation, Mm
Never under 140	5	16.0
Never under 130	16	12.7
Never under 120	28	9.0
Never under 110	33	7.6
Never under 100	54	6.9
Under 100 in at least one reading	49	8.0

The average range of differences between the highest and lowest readings over a ten year span varies proportionately with the level of systolic pressure (table 5) At pressures over 140 mm there is a difference of 36 mm between the lowest and the highest reading, as compared with a difference of 19 mm at a level of 100 mm

2 Second, it was observed that blood pressures which were consistently low did not vary as much from year to year as those that were consistently high From table 6 one sees that the higher pressures were definitely more erratic from year to year than were the lower pressures

3 More illustrative than the simple average variation is the comparative percentage of each of the various groups which registered high

31 A complete statistical analysis of these continuous records will appear in a subsequent publication

yearly ranges. Notice (table 7) that the persons who consistently showed high pressure over a span of years usually showed greater variation than did persons who consistently showed low pressure (chart 3). Comparison of another random sample of 15 men who *always* registered pressures over 120 mm with 15 men who *never* registered pressures over 120 mm showed an excess of 14 mm in total range and of 4 mm in mean range in the former group (chart 4). Further, the group with systolic pressures above 120 mm showed a definite tendency to increased pressure with age while the group with systolic pressures below 120 mm kept a constant level.

4. The fact that as pressures increase they tend to show wider variation suggests that the genesis of hypertension will show itself in transient elevation of pressure. A person usually does not become hypertensive suddenly, nor does the blood pressure rise steadily each year to higher levels. There is usually an ever increasing number of temporary excursions into higher levels. The effect of these temporary

TABLE 7—*Degrees of Variation in Blood Pressure*

Systolic Pressure, Mm	Percentage of Group Showing a Total Variation of			
	More Than 20 Mm	More Than 25 Mm	More Than 30 Mm	More Than 40 Mm
Always over 140	100	80	80	20
Always over 130	67	56	33	11
Always over 120	57	48	26	9
Always under 120	33	27	13	0

excursions is cumulative, the pressure continuing at a high level with only momentary lapses into low pressures. "The highest readings must not be disregarded."³²

In observing a list of persons whose records are available for ten or more years, it was noticed that if the systolic pressure during the first years even once reaches a level above 130 mm it is almost certain that that pressure will be exceeded before the tenth year is passed. For example, in the case of S. R. B., a man aged 43 whose pressure in 1928 was 134 mm, the systolic blood pressure was lower for the next two years, in 1931, however, it was 136 mm, and in 1933 it was 140 mm. It varied from 130 to 140 mm until 1938, when it was 156 mm. An even more striking example is the case of E. L. M., a woman who at 53, in 1927, had a systolic pressure of 140 mm. In 1928 the systolic pressure was 122 mm. It varied around 130 to 140 mm for the next four years, but in 1933 it rose to 146 mm. Some physicians would consider a pressure of 146 mm as "normal," but the next three annual readings

³² Bolt, W. Hypertension as an Underwriting Problem, Proc. A. Life Insur. M. Dir. America 21:183, 1934.

ranged from 154 mm to 220 mm , in 1938, at which time she had a stroke E L M's systolic pressure of 122 mm in 1928 was not normal (table 8)

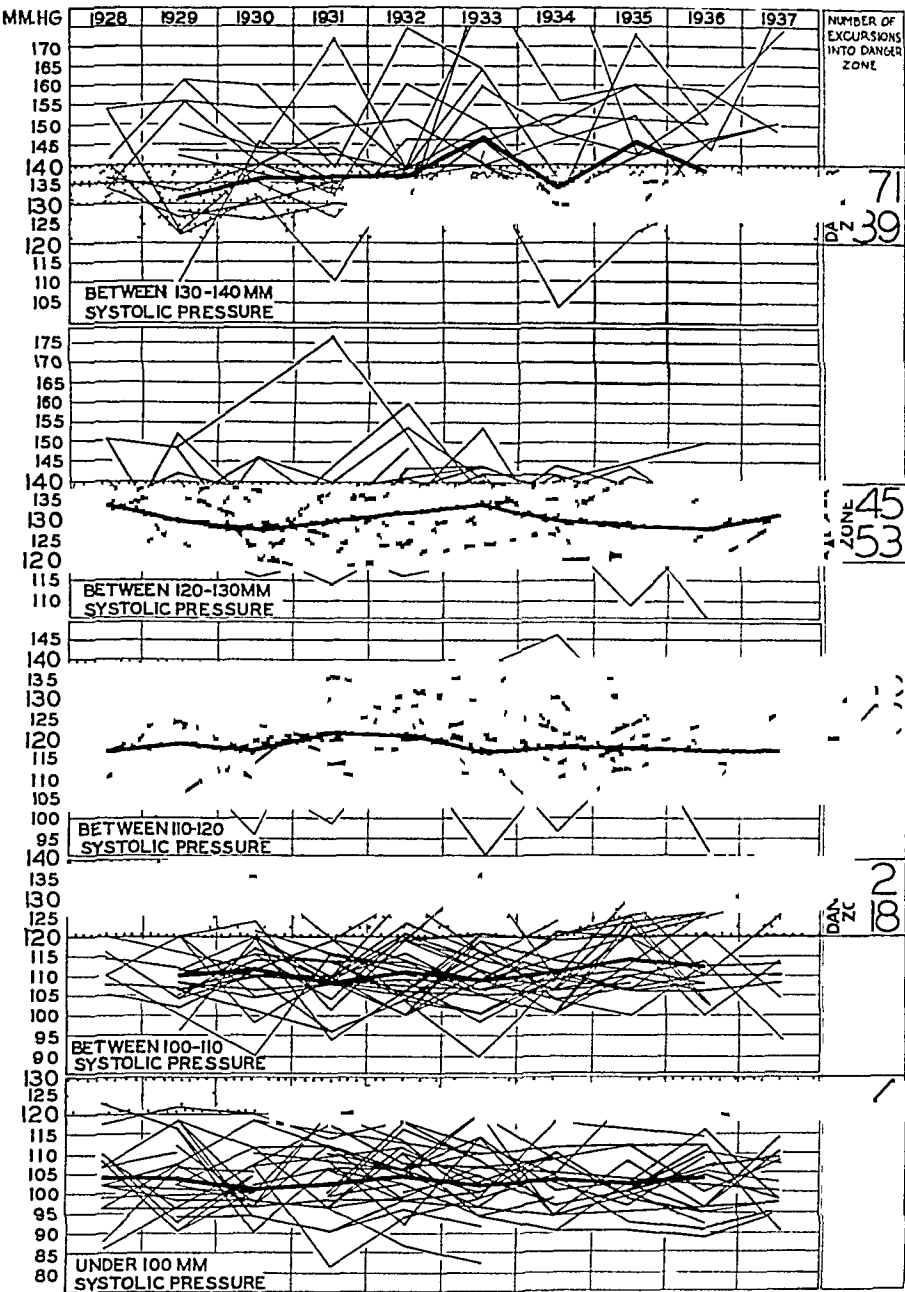


Chart 3—Study of ten year continuous records The five types of pressure records indicated in the graph were selected Note that the lower pressures tend to maintain their levels and show smaller and less erratic variations As the pressures increase the excursions into the danger zone become more frequent

These observations are at complete variance with those of investigators who brush aside an occasional high reading. To quote one example, Stieglitz³³ stated "Minor fluctuations of 15 to 20 mm of pressure occurring under conditions of psychic strain are normally physiologic." We find that in most instances a "minor fluctuation" is the forerunner of hypertension. No data are available in the literature, so far as we can find, to support the opinion that minor fluctuations are normal. The only work that deals with the subject supports our results³⁴.

As it becomes increasingly evident that the blood pressures which show intermittent excursions to high levels are those that lead to hypertension in later years, it would be interesting to find at which levels the blood pressure is most likely to make these transient excursions. In

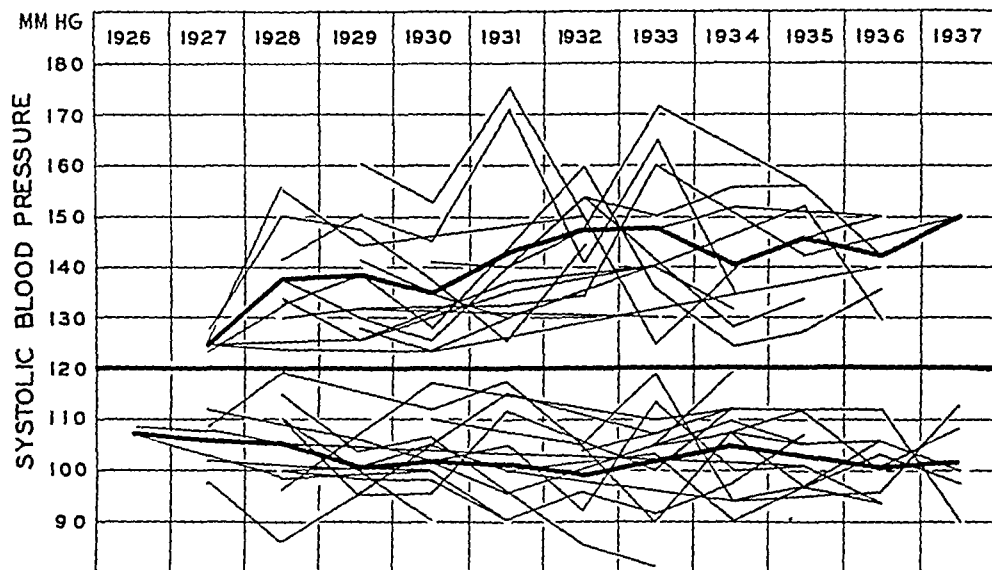


Chart 4—Comparison of pressures always above 120 mm systolic with those always below 120 mm over a ten year span. This graph shows the tendency of systolic pressures which always remain under 120 mm of mercury to maintain a steady level, with smaller and less erratic variations. The pressures which always register above 120 mm tend to have greater and more erratic variations, with a tendency to rise with age.

order to study this problem, we divided a part of our continuous records into five groups, according to the frequency with which the lower read-

33 Stieglitz, E. J. Emotional Hypertension, *Am J M Sc* **179** 775, 1930, footnote 13.

34 (a) Diehl, H. S., and Hesdorffer, M. B. Changes in Blood Pressure of Young Men over a Seven Year Period, *Arch Int Med* **52** 948 (Dec) 1933. (b) MacKenzie, L. F. The Significance of Hypertension, *Proc A Life Insur M Dir America* **24** 157, 1937. (c) Palmer, R. S. The Efficacy of Medical Treatment in Essential Hypertension, *New England J Med* **215** 569, 1936. Bolt³².

TABLE 8—*Ideal Blood Pressures and Blood Pressures Indicating Incipient Hypertension*

Age at First Examination	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938
							Ideal Blood Pressures						
32	112/84	114/70	100/68	100/70	98/70	102/78	98/70	92/68	100/74	104/74	108/68	92/68	
47		100/66	100/64	106/68	100/70	103/72	104/72	90/58	98/66	106/70	100/60	106/68	84/68
57	104/68	102/68	106/66	108/68	100/70	100/72	110/74	118/68	94/77		104/70	98/68	
64			102/74	110/66	102/70	102/58	118/70		108/64	110/66	104/70		108/72
55		128/62		124/72	110/68	98/70	122/68	120/60	122/64	112/60	120/72	110/78	
							Incipient Hypertension						
40		134/94	126/90			136/88	130/86	110/98	130/92	140/100	132/104	142/102	156/96
66			110/74	146/86	136/72	132/70	146/82	132/74	142/76	114/78	114/86	136/80	
42				136/90	120/70	132/76	122/80	134/84	160/78	148/80	112/80		140/82
29		132/80			132/92	140/84	136/80	130/78	126/78	140/90	122/82	136/86	144/88
38				140/78	152/70	138/70		134/70	154/78	126/75	120/72	142/72	

ings were obtained (chart 3) We then designated the levels of from 120 to 130 and 130 to 140 mm systolic as danger zones of potential and actual hypertension Persons whose systolic blood pressure periodically dips under 100 mm only rarely enter the danger zone As the level of pressure increases the excursions into the danger zones increase

It seems evident that systolic pressures which regularly are above 120 mm are bound to show transient elevation into the danger zone of 130 to 140 mm The physiologic effect of these frequent daily periodic excursions into hypertensive levels may be the early groundwork of incipient hypertension Because blood pressures are not static, a man whose systolic pressure does not dip below 120 mm on successive readings must be potentially hypertensive This is obvious when one takes into consideration his usual 15 mm of diurnal rhythmic flux of pressure Systolic pressures above 120 mm are in the zone of hypertension, and transient elevations into the danger zone are an indication of incipient hypertension A systolic blood pressure above 120 mm cannot under these conditions be correctly considered "normal" To be sure one may not be able, with the present limited knowledge, to find objective evidence of pathologic change, but such a pressure does indicate the probable genesis of long, drawn-out disease

5 Another, and probably the most important, finding is apparent among persons with low blood pressure, i e., the tendency of systolic pressures below 120 mm to maintain an even course throughout life Low blood pressures rarely change their level in the direction of a steady rise Of over 200 continuous low blood pressure records only 2 indicated an increase with age From these lines of evidence it seems wholly justifiable to conclude that persons with low pressures continue at these levels throughout their lives, while those with moderately high pressures tend to have much higher pressures, usually after the age of 40 (chart 3)

Summary—It is seen how the study of the life history of vascular tension gives a new impression of blood pressure It introduces the concept of blood pressure as a dynamic physiologic force, and through the aid of this concept one comes to a comprehension of the growth, the maturity and possibly the senescence of that force The blood pressure undergoes continuous change throughout the twenty-four hours of each day Statistical studies on isolated blood pressure readings are forced to treat these readings as static phenomena It is undoubtedly important to be aware of the general level of blood pressure in large groups of persons, but it is far more important to know the surging and resurging flow of the ever changing compensations in pressure in persons who do and in persons who do not have hypertension We have shown that there is a difference in the daily changing tensions of the vascular system in the healthy and in the prehypertensive person We have shown that pressures under 120 mm are less variable and less

erratic than are pressures continuously over 120 mm and that transient excursions into the danger zones of hypertension are rare in persons with low pressures. Further, pressures under 120 mm tend to maintain a constant level, while those over 120 mm rise with increasing age. We conclude from this study of continuous records that the range of normal systolic blood pressure must not extend above an upper limit of 120 mm.

MORTALITY RATE AT DIFFERENT BLOOD PRESSURE LEVELS

The next problem that logically follows a study of the life history of blood pressure is the mortality of persons with different levels of tension. This death record provides a natural confirmation of the long term trends of different blood pressure levels observed during life. It is essential that the physician know where he stands in the control of morbid processes, he cannot pronounce persons "normal," "healthy," or "free from disease," unless he is constantly aware of the factors which shorten life and of those which contribute to long life. The physician's most accurate check on the potential longevity of his patient is the patient's deviations from physiologic norms. Mortality statistics place the patient in the perspective of potentiality. When the level of a clinical measurement falls in a category with an extremely high mortality rate, obviously that level is abnormal and the patient is not "healthy," no matter how well he feels. For example, when we learn that excessive weight is associated with a terrifically high mortality, almost pound for pound, even the moderately overweight person must be considered abnormal. The same is true of the pulse rate, for which the norm, for generations fixed at 72 ± 10 beats per minute, is found in the light of mortality studies to be associated with a higher death rate than is a pulse rate of 50 to 65. To the physician this should mean (chart 5) that the norm is too high.³⁵

With blood pressure, as with weight and pulse, one should look on the mortality rate as a check on the levels one accepts as normal. From our statistical study and our continuous records we decided that 120 systolic and 80 diastolic are "upper limits." This cannot be true unless it checks with the best mortality rate. In chart 5 we find complete accord with our conclusions. With a rise in blood pressure there is an abrupt rise in the death rate. This rise begins with the very low pressures. By no stretch of the imagination can pressures of 130 to 140 mm be considered normal. Diastolic pressures over 80 mm are associated with an increase in the death rate that is not compatible with the word "norm."

³⁵ Sydenstricker, E. Physical Impairment and Occupational Class, *Pub Health Rep* **45** 34, 1930. Morgan, P. W. The Status of Persons with Sinus Bradycardia, *J. Kansas M. Soc.* **37** 455, 1936.

Most medicoactuanial experience with blood pressure levels speaks in favor of low pressure. The Northwestern Mutual Life Insurance Company²³ⁿ found a mortality ratio of 35 per cent for pressures under 100 mm as compared with 94 per cent for pressures averaging 142 mm and 114 per cent for pressures averaging 153 mm (table 9). There was a steady increase in mortality with increase in pressure. Fisher³⁶ (table 10) cited a mortality study which corroborated this step like rise in mortality with increase in pressure³⁷.

The records of the Prudential Life Insurance Company¹⁷¹ (table 11) show that low mortality rates fall in a classification of an underaverage diastolic blood pressure, though the authors of the report, MacKenzie

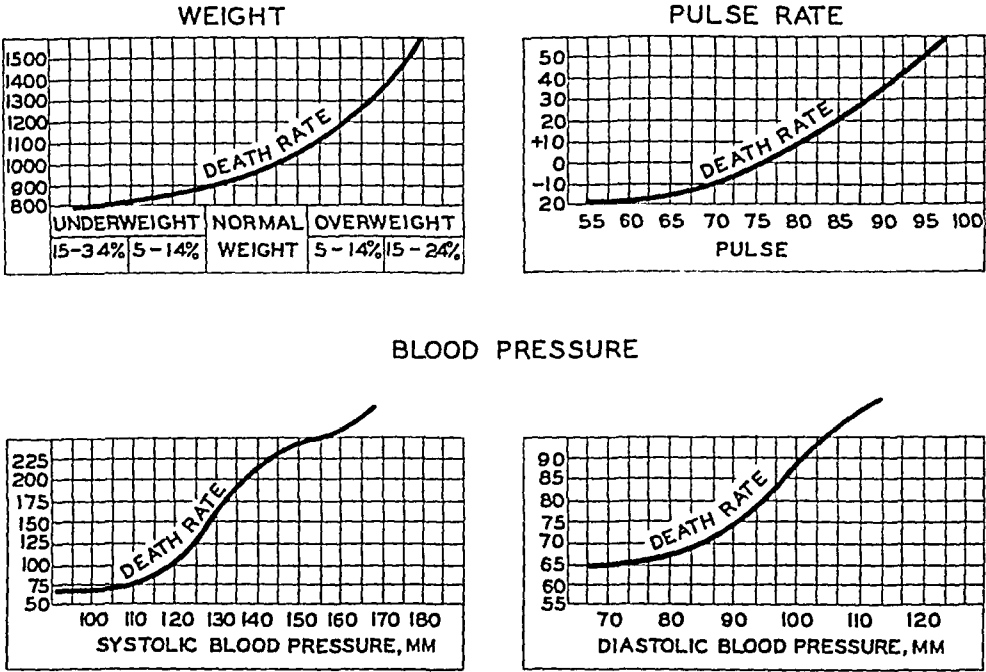


Chart 5—Mortality trends for various physiologic measurements, showing in all cases that the higher readings are accompanied by a rapidly mounting death rate. The low readings are the most desirable, in all measurements they are associated with the lowest mortality. The weight curve was modified from Dublin and Lotka,^{1a} tuberculosis being excluded. The pulse curve was adapted compositely from P. W. Morgan (Morgan, P. W. The Status of Persons with Sinus Bradycardia, J. Kansas M. Soc. **37** 455 [Nov.] 1936), Rogers and Hunter^{5t} and Dublin and Lotka^{1a}. Blood pressure curves were derived compositely from statistical material cited in the section on mortality.

and Wells, did not agree with the preceding authors in regard to the favorable mortality rate of the very low systolic pressures. Living-

36 Fisher, J. W. Report of Committee on Low Blood Pressure, Proc. A. Life Insur. M. Dir. America, 1917, p. 204.

37 Fisher, J. W. Use of Sphygmomanometer, Proc. A. Life Insur. M. Dir. America, 1907-1912, p. 393.

ston³⁸ also found a slightly higher mortality with the very low systolic pressures, but even so it is 13 per cent lower than the average. Thus, as both systolic and diastolic pressures are similarly disposed as to mortality rates, one would expect that the combination of systolic and diastolic pressures would produce a similar disposition. Bolt³² confirmed this in a study of "mean" blood pressure $\frac{(\text{systolic} + \text{diastolic})}{2}$ and stated³⁹ "Our New York Life experience shows mortality directly proportional to the high readings. *There are too many physicians who underestimate the seriousness of a moderate elevation of pressure*"

TABLE 9—*Experience of Northwestern Mutual Life Insurance Company**

Range of Arterial Tension	Ages at Entry	Ratio of Actual to Expected Mortality, %
Low blood pressure (100 mm and under)	16-60	33
Average blood pressure of 142 mm	40-60	90
Average blood pressure of 153 mm	40-60	115

* Expected mortality, 80 per cent

TABLE 10—*Life Expectation of Persons with Hypertension (American Actuarial Society)*

	Percentage
Expected deaths according to American actuarial tables	100
Pressures of 105 mm and under	47
Pressures of 106-100 mm	65
Usual experience with accepted risks	86
10-14 mm over average pressure for age	114
15-24 mm over average pressure for age	181
25-34 mm over average pressure for age	205
35-44 mm over average pressure for age	246
45-49 mm over average pressure for age	254
60 mm and more over average pressure for age	450

Dublin and Lotka,^{1a} Southby,⁴⁰ Fraser,⁴¹ Muhlberg,⁴² Brown⁴³ and Rogers and Hunter^{5f} unanimously confirmed this conclusion.

The most extensive investigation of the relation of mortality to blood pressure was made by the Joint Committee on Mortality of the Associ-

38 Livingston, J. M. Blood Pressure Normal and Abnormal, Canad M A J 30 54, 1934

39 Bolt, W., in discussion on MacKenzie^{34b}

40 Southby, R. Clinical Observations on Blood Pressure with Special Reference to Variation of Blood Pressure Readings in the Two Arms, M J Australia 2 569, 1935

41 Fraser, R. A. Life Insurance in the Service of America's Health, Proc A Life Insur Pres 28 53, 1934

42 Muhlberg, W. Medical Resources and Mortality Trends, Proc A Life Insur Pres 27 142, 1933

43 Brown, in discussion on Rogers and Hunter^{5f}

44 Footnote deleted by author

ation of Life Insurance Medical Directors and the Actuarial Society of America. The report of this committee was an analysis of the records of 707,000 policy holders, which were submitted by twenty-six leading insurance companies in the United States and Canada. The Joint Committee on Mortality^{23b} concluded that the underaverage pressures were associated with a lower mortality than was the "average" pressure in every age group (table 12). Hay⁹ aptly summed up these findings in his statement: "There is something dramatic and ominous in the steady diminution in the expectation of life accompanying a rise of blood pressure."

It seems that mortality studies are in complete accord in condemning the popular notion that low blood pressure is a disease and moderately

TABLE 11—*Ratio of Actual to Expected Mortality Rate (American Men's Standard) for Standard Risks According to Diastolic Pressure (Prudential Life Insurance Company)*

Ages at Entry	Under 70 Mm	70-79 Mm	80-89 Mm	90 Mm and Over
15-29	60	77	100	104
30-39	47	67	64	81
40-49	47	55	63	60
50 and over	26	25	60	62
All ages	49	61	69	72

TABLE 12—*Ratio of Actual to Expected Deaths for All Ages According to Pressure (Joint Committee on Mortality)*

	Underaverage 5 to 15%	Average	Overaverage 5 to 15%
Systolic	94%	100%	114%
Diastolic	94%	100%	116%

high pressures are "normal" and safe.⁴⁵ Part of the definition of a normal person is that he must live long, be relatively free from illness and not be prematurely killed off by degenerative diseases. Invariably this is the person with a low weight, a low pulse rate and a low blood pressure.⁴⁶ This triad of physiologic levels is the foundation stone on which longevity is built. Symonds,^{46b} in his widely quoted work on

45 Garvin, J. D. Hypotension. Report of Six Cases in One Family, *J. A. M. A.* **88** 1875 (June 11) 1927. Friedlander, A. Clinical Types of Hypotension, *ibid.* **83** 167 (July 19) 1924. Roberts, D. M. Hypotension or Low Arterial Pressure, *Illinois M. J.* **71** 448, 1937. Brower, A. B. Hypotension, *Ohio State M. J.* **33** 152, 1937. Blackford, J. M., Bowers, J. M., and Baker, J. W. Follow-Up Study of Hypertension, *J. A. M. A.* **94** 328 (Feb. 1) 1930. Lewis, T. *Diseases of the Heart*, ed. 2, New York, The Macmillan Company, 1937.

46 (a) Gregory, J. R. Variations in Blood Pressure and Their Clinical Significance, *East African M. J.* **14** 3, 1937. (b) Symonds, B. Blood Pressures of Healthy Men and Women, *J. A. M. A.* **80** 232 (Jan. 27) 1923.

blood pressure, stated "It would seem that the average pressure runs counter to the best interests of health" The Joint Committee on Mortality^{23b} expressed agreement "The average blood pressure does not seem to be the pressure of lowest mortality" The normal person is the person with a blood pressure below average In other words, the established "average," or normal, pressure of today is too high

Summary—These mortality records from a variety of insurance companies all agree that pressures over 140 systolic and 90 diastolic are definitely associated with a proportionately increased death rate They all agree further that a higher mortality is to be expected among persons with pressures of 130 systolic and 80 diastolic than those in the pressures of 120 systolic and 80 diastolic Many go further and show that a pressure of 110 systolic and 70 diastolic is associated with a lower mortality rate than one of 120 systolic and 80 diastolic Some of the companies indicate that pressures below 110 systolic and 70 diastolic may have the best mortality rate In general, the mortality of any random group of 1,000 persons with pressures over 120 systolic and 80 diastolic is higher than that of a similar group with pressures under these levels

COMMENT

The status of knowledge concerning blood pressure is such that the wide divergence of authoritative opinion as to what constitutes "normal" has given rise to much confusion The upper level of normal systolic pressure, according to contemporary literature, can extend from 120 to 160 mm, the diastolic limits, anywhere from 90 to 110 mm However, during the past decades the preponderance of opinion regarding normal levels has shifted toward lower limits The confusion which invariably results from a shifting level has made itself felt in recent medical texts Many authors do not commit themselves as to normal levels, and those who do take a stand give two levels, with a "no man's land" between Moreover, the tendency to establish norms and then disregard them seems indicative of growing uncertainty of the norms which were established It is, of course, dangerous for an author to commit himself to a fixed norm in the face of conflicting opinion, but in no field of modern medicine is there greater need for clarification than in that of blood pressure We feel strongly that it is dangerous even unwittingly to evade the paramount issue of narrowing the extremely wide range that now exists for normal blood pressure

We have attempted to explain in detail the reasons why such confusion exists We have further pointed out that all past studies relied too exclusively on statistical data Such studies have value, but in order to arrive at any physiologic norm it is necessary, in addition, that

an analysis of the life history of the measurement be made and then correlated with mortality data. The interplay of all of these factors must be taken into account before one can establish a physiologic norm.

We have shown that it is statistically as well as physiologically in error to group together for study normal and pathologic subjects in order to arrive at normal levels. Such a study will give the sum total of the data for both groups. Our study has taken full cognizance of the inherent danger of such a mixed group and accordingly has, at the outset, discarded the obviously hypertensive subjects, whose presence has led so easily to misinterpretations of "normal" in the past.

We have, however, submitted the data on our total group with several breakdowns of statistical treatment (table 1) for those who are especially interested or who wish to make comparisons with other existing data.

The only valid and significant conclusions that we were able to draw from our total group related to diastolic blood pressure. Most previous studies of blood pressure have established 90 mm as the upper limit of normal, some giving 95 and others 100 mm and over. From a study of our total group, a statistical analysis alone, without inclusion of other data (which we look on as absolutely essential in arriving at norms), we place the upper limit of normal diastolic blood pressure at about 80 mm.

The first step in our statistical analysis was to eliminate the obviously hypertensive subjects. We decided to eliminate all readings above 140 mm systolic or 90 mm diastolic as definitely pathologic, since this was a level accepted by many recent writers. Slightly more than one tenth of our subjects were discarded as grossly hypertensive, but by no means did we eliminate all of the hypertensive persons. As was shown later, many were included. The statistical analysis was completed on this delimited section of the total—a smaller, select sample, more nearly normal than any total group.

Study of this delimited group shows that men usually have a blood pressure of 115 ± 10 mm systolic and 72 ± 8 mm diastolic, women show pressures of 112 ± 10 mm systolic and 70 ± 8 mm diastolic. These facts should indicate that the upper limits of blood pressure must be under 125 systolic and 80 diastolic. We further showed to be true what a few astute observers⁴⁷ have long believed, that normal blood pressure does not rise with age. We confirmed in this study of the delimited group the findings of some previous workers that young women have lower pressures than young men and showed that older women have substantially the same, or slightly lower, pressures than older men.

47 Stocks, P, and Karn, M. N. *Blood Pressure in Early Life*, London, Cambridge University Press, 1924. MacWilliam³⁰ Alvarez^{17c} Dingman^{17j} Hunter¹⁶ Huber^{17g}

These conclusions were drawn from analyses of static statistical tables, but blood pressure is so overwhelmingly a dynamic process that a study of the flux of pressure levels over a period of years was felt to yield far more important results. No study can be complete unless the life history of blood pressure is taken into account. Therefore, we analyzed a group of 500 records continuous over a period of five to ten years.

When we followed the course of blood pressure in its aberrations over a period of years, we noticed first the year to year variations. Much of this variation, it was decided, is due to the normal diurnal flux of pressure, which emulates temperature, pulse and the diurnal harmonics of metabolism. A second observation was that the lower pressures did not show as great a variation—usually it was less than 10 mm, while the higher pressures usually varied by 15 to 40 mm. Third, low pressures almost invariably tended to remain at the same general low level throughout all age groups, while the higher pressures showed definite signs of rising to even higher levels with advancing years. It was shown that blood pressure readings persistently below 120 mm remained at the same level throughout a ten year period in any age group and had little variation, while systolic blood pressures persistently above 120 mm showed a tendency to rise over a ten year span in all age groups and showed greater and more erratic variation. From these continuous records we concluded that normal systolic blood pressure should not exceed 120 mm.

It was further shown that once a person's pressure shows even intermittent rises into the danger zones of 120 to 130 and 130 to 140 mm it frequently returns to that level. We suspected that these excursions into the danger zone tended to become more and more frequent and considered these pressures as indicating incipient hypertension.

Another important measure available for a check on the norms is a study of mortality data. The word "normal" is inconsistent with a high mortality rate. Whatever the method of selecting any physiologic norm, the level cannot be interpreted medically as "normal" unless it is consistent with the longest possible life.

What is the vascular tension that leads to the longest life span, and what are the levels that shorten life? This question is of the greatest interest in our study because it forms a background for our definition of "normal." There is overwhelming evidence from available actuarial material that shows increased mortality to be directly proportional to increased blood pressure. And what is of the greatest significance is that the increase commences at below average levels. In other words, men with blood pressures of 120 mm and over will die sooner than men with blood pressures under 120 mm. It is thus seen that mortality data completely corroborate the low levels of blood pressure, i. e., under 120 systolic and 80 diastolic, which we have established as normal.

It can be seen from these new levels of blood pressure that there is now an entirely different picture of hypertension, which fits in far more coherently with the picture of hypertensive heart disease and its high death rate. The incidence of high blood pressure is much higher than is generally realized, about 40 per cent of the adult population is prehypertensive or hypertensive. Hypertension is a long term disease, not a short term degeneration beginning after the fortieth year, almost as many young persons as old persons have potential or actual high blood pressure, the only difference being in the severity of the condition. Hypertensive heart disease starts during youth, and its diagnostic sign is a persistent elevation of blood pressure into levels over 120 systolic and 80 diastolic, frequent intermittent excursions above these levels denote incipient hypertension.

We have stressed the flux, or movement, and variability of blood pressure. This seemed to indicate that when one looks for normal levels one must consider the task as one not merely of selecting a fixed point—120 or 130 mm—but of picking a range of blood pressure readings within which normal surging movement of vascular tension takes place. One cannot expect to interpret the phenomenon of a fluctuating pressure head moving within viscous fluid down a branching system of elastic tubes on the basis of a single static number. The very nature of blood pressure is movement, and in the future blood pressure must be designated as a range of movement. Much of the older work has seriously handicapped the usefulness of the sphygmomanometer by giving physicians the impression that man's blood pressure should be fixed at a static level of 120 or 130 mm. Blood pressure must be interpreted as a range of systolic and a range of diastolic pressure. If one records a patient's blood pressure for the first time at 120 mm, he may be either hypertensive or normal. If over a period of years the 120 mm reading is the lowest pressure, he is hypertensive, if it is the highest pressure, he is normal.

In the face of a value which is in constant variation, it is easy to see why some investigators have given up the hope of establishing norms for blood pressure. Dr Clarence L. Andrews, in a talk before the American College of Physicians, stated that "there is no such thing as 'normal' pressure at any period of life, what is normal for one man may indicate disease for another." This is a dangerous axiom that is gaining ground in current medical thought. No abnormal physiologic level is normal for any given person. No person can carry higher than normal physiologic levels with impunity. Men die sooner if the pulse rate, the temperature, the weight and the blood pressure are only slightly elevated above the established "normal" levels. An occasional exception must not sidetrack one from the immutable laws that inevitably lead the overwhelming majority of persons with abnormal readings to an early death. After all, these physiologic levels have been fixed over millions

of years of evolutionary ascent. The range of blood pressure must be considered to be as immutable and as constant as the temperature and pulse rate. If by "normal" one means the probability of a long life, a low morbidity rate and efficient activity, it is almost obvious that there is a normal-healthy range of blood pressure and an abnormal, diseased range.

Who is the normal person? Surely he is one who is free from disease, discernible or latent—one who is subjectively well. The fact that he has no latent disease is learned through a consideration of simple clinical tests. However, these clinical tests in almost every category have described a range of "normal" far too wide and not consistent with the best mortality rates, and physicians have begun to whittle away at the extremes of these too wide ranges. Compare the standard weight tables of twenty-five years ago with those published today. Statisticians formerly allowed more weight than can now be conceded even to civilized man, and allowed an increment with an increase in age. It is generally accepted now that optimum weight remains constant after maturity is reached, at about the age of 30. The same process of revision is discernible in all physiologic measurements. The pulse rate is no longer considered normal at 90, nor is the temperature at 99.6 F. Blood pressure, blood sugar and basal metabolic rates will all be allowed less range in the future. All of these measurements require revision, and revision chiefly downward.

The "normal" that will be selected must be compatible with a long and healthy life. Physicians are beginning to realize that the below average levels are associated with a lower mortality than are the average and therefore are the truly normal levels. This can mean only one thing. Many now acceptable "normal" persons are in reality museums of incipient disease.

It is significant that the pressures now accepted as normal are close to what was once called "hypotension."

It is ironic that since the invention of the sphygmomanometer physicians have attempted to discover some pathologic condition to explain low pressure, the truly normal and ideal range of blood pressure, and have neglected to recognize the ominous character of potential hypertension. As a result, thousands of normal persons are treated for hypotension, and a much larger group in the hypertensive class are given a false sense of security.

Much work is necessary in all fields of blood pressure research. There are necessary more studies of static pressure readings, taken under rigidly standardized conditions, for different social and occupational groups. More important is the need for detailed studies on records continuous over a period of years and on the comparative mortality of persons with various levels of pressure. We hazard the

guess that when the final data are available any changes in the level we have proposed for normal blood pressure will be in the direction of lower limits

CONCLUSIONS

1 A new and more rational range of normal blood pressure is postulated as the result of (1) a statistical study of 10,883 persons, (2) a study of five to ten year continuous records of 500 persons and (3) an appraisal of mortality at various pressure levels

2 The normal range of systolic blood pressure for men and women is from 90 to 120 mm of mercury

3 The normal range of diastolic blood pressure for men and women is from 60 to 80 mm of mercury

4 A normal person attains his mature blood pressure at about adolescence and keeps that range throughout life, except for a slight rise at about the twentieth year

5 Normal blood pressure does not rise with age Prehypertensive and hypertensive pressures do rise with age

6 "Hypotension" is neither a disease nor a disease entity, it is an ideal blood pressure level In the absence of other findings this is true of pressures that occasionally dip to the level of 80 systolic and 50 diastolic

7 The commonly described symptoms of the disease called "hypotension" can be ascribed with equal statistical accuracy to any level of blood pressure

8 Blood pressure should be considered a physiologic measurement in continual diurnal flux, highest during the afternoon, lowest during the early morning hours

9 The daily and yearly variation of normal blood pressure is from 5 to 10 mm of mercury

10 Higher levels of blood pressure show proportionately greater and more erratic yearly variations

11 Lower levels of blood pressure show smaller and less erratic yearly variations

12 A blood pressure history is more nearly normal as it shows occasional pressures below 110 systolic and 70 diastolic

13 A person who has a history of pressures which occasionally dip to the 90 systolic and 60 diastolic level, or even to the upper part of the 80-90 systolic and 50-60 diastolic range, has an added assurance of not becoming hypertensive

14 A blood pressure history of over 120 systolic and 80 diastolic over a ten year span in a man or woman is pathologic, and is an almost infallible sign of incipient hypertension Once a pressure is definitely established in this range it seldom if ever will become normal

15 Transient elevations of blood pressure should not be ignored. They should be suspected of a further, more frequent and possibly permanent rise.

16 Moderately high blood pressures are incipiently hypertensive.

17 Persons with hypertensive heart disease are recruited from persons with incipiently hypertensive blood pressure levels.

18 High blood pressures tend to become even higher, the higher pressures invariably resulting in hyperpiesia.

19 High blood pressure is a long term disease having its genesis at an early age. It is not a disease that suddenly emerges with middle age.

20 Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive.

21 A study of any normal physiologic measurement must check with mortality data. One of the criteria for the selection of a normal range is that it be compatible with the lowest possible mortality and the longest life span.

22 The mortality rate increases progressively with an increase in systolic or diastolic blood pressure.

23 Persons with low blood pressures have the lowest mortality rate. Those with blood pressures persistently over 120 mm of mercury systolic and 80 mm diastolic have a higher mortality rate than those with blood pressures persistently under 120 mm systolic and 80 mm diastolic.

Mrs Mary Neil collected data used in this study over a period of years. Dr Dudley B. Reed supplied data from the files of the Student Health Service of the University of Chicago. Data from the health service of the West Side Y. W. C. A. were made available by Dr Rudla Rind. Dr Louis W. Desprez cooperated in connection with the study of continuous records, and Dr Anthony N. Trapp secured additional continuous records. Mr Walter Bittner assisted with the editing of the manuscript. The University of Chicago furnished office space. The statistical labor was performed with the aid of the Works Progress Administration. The project was under the sponsorship of the Institute for Juvenile Research, Dr Paul L. Schroeder, director. Mr R. A. Wolff, Mr Walter Majewski and Miss Florence Duryea assisted with the statistical investigation.

BILIRUBIN AND UROBILIN CONTENT OF BILE OBTAINED BY DUODENAL DRAINAGE

NORMAL VALUES AND VALUES FOR PATIENTS WITH CHOLECYSTITIS

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Study of the bile obtained by means of duodenal drainage in man can give significant data regarding inflammation of the gallbladder. For instance, the presence of desquamative elements originating in the biliary tract (cells, leukocytes) is important evidence of cholecystitis. The difficulty at times consists in deciding whether the elements have come from the gallbladder, the extrahepatic bile ducts or the liver. This applies also to the presence of albumin in the bile. Faulty evacuation of the gallbladder is a sign which is present in cholecystitis, as it is a negative sign and appears in association with other diseases also, it is of much less importance.

Since cholecystitis is a common disease, it is useful to have multiple methods for its diagnosis. For many years I have studied the possibility of making a diagnosis of cholecystitis on the basis of the concentration of the bile pigments bilirubin and urobilin. In 1933 I¹ published my first results, which were later confirmed by Castex and López García².

In this paper I propose to describe first the normal behavior of bilirubin and urobilin in normal bile, clinically and experimentally. Later the same pigments will be considered in relation to pathologic states.

TECHNIC

The bilirubin content was determined as follows. The bile to be tested was mixed with acid alcohol³ in different proportion (1:10 to 1:50) according to its concentration. Eighteen to twenty-four hours later the mixture was examined with the photometer of Pulfrich, with the filter S66, 613,5, the factor 25 being used as a constant. The difference between the readings for the two drums was multiplied by 25 and by the titer of the dilution. The final result gave in milligrams the concentration of bilirubin per liter. The control readings gave errors not greater than 4 to 5 per cent.

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1 Royer, M. Les pigments de la bile obtenue par tubage duodenal. Leur importance dans le diagnostic des cholécystites, *Presse med* 41:74, 1933.

2 Castex, M. R., and López García, A. La urobilina en el líquido duodenal, *Bolet Acad nac de med de Buenos Aires*, 1934, p 128.

3 Acid alcohol is a mixture of 0.4 cc of concentrated nitric acid, 22 cc of concentrated hydrochloric acid and 100 cc of 96 per cent alcohol.

The urobilin content of the bile was measured by means of the method I⁴ described in 1928, which is a modification of the one published by Elman and McMaster⁵ in 1925, the fluorescence being measured. Later (1932) I⁶ modified it for clinical use.

NORMAL STATE IN MAN STUDIED BY DUODENAL DRAINAGE

A study was made by means of duodenal drainage of 25 persons with normal biliary tracts. Only A bile and B bile were considered (table 1), C bile may, for the present purposes, be taken to be like A

TABLE 1—*Bile Pigments Obtained by Duodenal Drainage from Patients with No Lesions of the Gallbladder*

Case No	Condition	Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		In A Bile, Mg per Liter	In B Bile, Mg per Liter	Coeff-icent of Increase	In A Bile, Mg per Liter	In B Bile, Mg per Liter	Coeff-icent of Increase	
1	Normal	42.0	65	1.5	0.34	0.36	1.0	1.5
2	Typhlitis, constipation	40.0	142	3.0	0.24	0.46	1.9	1.5
3	Cancer of esophagus	131.6	207	1.5	1.12	1.29	1.1	1.3
4	Ovarian insufficiency	28.5	360	12.6	2.10	10.33	4.9	2.5
5	Serofibrinous pleurisy	92.2	423	4.4	0.99	1.53	1.3	3.4
6	Gastritis	60.0	185	3.1	1.12	3.63	3.3	0.9
7	Dyspepsia	121.0	519	4.2	1.53	2.96	1.9	2.2
8	Spondylosis, 2d lumbar vertebra	18.0	125	6.9	1.69	3.36	1.9	3.6
9	Metrosalpingo oophoritis	10.0	86	8.6	0.34	1.85	5.3	1.6
10	Hyperthyroidism	42.0	103	2.5	1.89	1.53	—0.8	3.3
11	Chronic bronchitis	20.0	105	5.2	0.61	0.81	1.3	4.0
12	Dolichocolon	15.0	165	11.0	1.12	4.83	4.3	2.5
13	Headache	62.0	175	2.8	1.40	1.89	1.3	2.1
14	Gastric lesion	210.0	366	1.7	6.07	9.06	1.4	1.2
15	Hepatitis	80.0	155	1.9	6.07	4.83	—0.7	2.6
16	Epilepsy	150.0	237	1.5	0.89	0.90	1.0	1.5
17	Gastric lesion	65.0	340	5.2	1.89	3.63	1.9	2.7
18	Hyperthyroidism	21.0	250	11.9	0.94	6.07	6.4	1.8
19	Hepatitis	62.0	118	1.9	3.36	4.83	1.4	1.3
20	Hemorrhagic pleurisy	87.0	137	1.5	0.46	0.50	1.1	1.3
21	Hepatitis	37.0	77	2.1	1.29	1.89	1.4	1.5
22	Vertigo	31.0	50	1.6	1.89	1.89	1.0	1.6
23	Fermentative colitis	300.0	975	3.2	3.36	6.07	1.8	1.7
24	Perityphlitis	131.0	425	3.2	0.81	0.88	1.1	2.9
25	Exophthalmic goiter	12.5	430	34.4	0.80	2.44	3.1	11.1

bile. From the data it can be seen that the bilirubin content of B bile was increased in comparison with that of A bile. The difference indi-

4 Royer, M. La urobilina al estado normal y patológico, Thesis, Buenos Aires, Frescol y Bindi, 1929, L'urobilina a l'état normal et pathologique. Étude expérimentale et clinique effectuée a l'Institut de Physiologie de la Faculté de Médecine de Buenos-Aires, Paris, Masson & Cie, 1930.

5 Elman, R, and McMaster, P. D. Studies on Urobilin Physiology and Pathology. I. The Quantitative Determination of Urobilin, J. Exper. Med. **41** 503, 1925.

6 Royer, M. Simplification de la méthode du dosage de l'urobilina, Compt. rend. Soc. de biol. **111** 825, 1932, El mesobilirubinógeno como patrón para dosar la urobilina, Rev. Soc. argent. de biol. **8** 489, 1932.

cated the degree of concentration of the bile by the gallbladder. The coefficient of increase is given in the table just mentioned. The urobilin content of B bile was also increased in comparison with that of A bile, but the coefficient of increase was much smaller than that for bilirubin except in case 6. This patient, unfortunately, was not reexamined, but his clinical history indicated that he may have had a lesion of the biliary tract.

These results can be explained if it is admitted that the bile stays a while in the gallbladder and becomes concentrated, owing to the absorption of water by the wall of the gallbladder. It is possible that bile pigments could be absorbed by the wall just as water is. If that is true, in order to explain the results obtained, it is necessary to admit that no bilirubin, or hardly any, is absorbed, this accounts for its high concentration in B bile. It must be admitted that in all cases urobilin is absorbed in greater amount than bilirubin, in order to explain the lower concentration of bilirubin in B bile. One of the reasons for believing that the absorption of urobilin is high in the gallbladder is that, in spite of the loss of water, the concentration of urobilin in B bile is lower than it is in A bile (see data for cases 10 and 15). In these conditions the ratio of the increase of bilirubin to the increase of urobilin will be over 1, in the present group of cases the values ranged from 0.9 to 1.1. An attempt was made to confirm experimentally the previous results.

EXPERIMENTAL STUDY OF BILIRUBIN

A study in the normal dog was made of the ability of both pigments to pass through the wall of the gallbladder. The first observation on this point was made apparently by Aschoff and Bacmeister⁷ (1909). They proved that under normal conditions bilirubin can be found in the wall of the gallbladder, owing to the fact that it is passing through the wall. Rous and McMaster⁸ (1921) deducted from their experiments on dogs that the bilirubin of the bile is not absorbed by the gallbladder. The objection to their experiments is that the exact amount of bile that entered the gallbladder could not be measured. Neither were they able to prove the presence of bilirubin in the efferent lymphatic ducts of the gallbladder. This last finding was verified by

⁷ Aschoff, L., and Bacmeister, A. *Die Cholelithiasis*, Jena, Gustav Fischer, 1909. Ivy, A. C. *The Physiology of the Gall Bladder*, *Physiol. Rev.* **14** 1, 1934.

⁸ Rous, P., and McMaster, P. D. *The Concentrating Activity of the Gall Bladder*, *J. Exper. Med.* **34** 47, 1921.

Riegel, Johnston and Ravdin⁹ (1932) But in 1924 Sweet¹⁰ found bilirubin in the lymph coming from the gallbladder Ravdin and Morrison¹¹ (1931) did not find bilirubin, either in the venous blood or in the lymphatic ducts from the gallbladder

Riegel, Johnston and Ravdin⁹ (1932) have studied the absorption of bilirubin by the gallbladder by employing an excellent technic A Nélaton catheter is inserted into the gallbladder by way of the hepatic duct, above the point where the ducts from the right and left hepatic lobules make their entrance Later the hepatic duct is fixed to the catheter in order to keep the latter in the desired place The other end of the catheter protrudes through a stab wound in the abdominal wall The operation is performed under aseptic conditions, and the animals live a long time The authors found it possible to study the animals without resort to anesthesia

To study the absorption of pigments they introduced into the gallbladder a certain amount of bile with a fixed proportion of bilirubin, a short time later (two to twenty-four hours) the gallbladder was emptied and washed, so that the exact amount of pigment contained therein could be accurately measured With this technic they observed in 7 of 18 cases a diminution of over 8 per cent (87 to 129 per cent) in the amount of bilirubin, the average for all the experiments was a diminution of 48 per cent In spite of their own results, the authors stated that they did not believe there was absorption of pigments by the gallbladder They used bile with such a high concentration of pigments that one wonders how they obtained it The concentration ranged from 0.32 to 2.2 Gm per hundred cubic centimeters All the values were well over what may be considered normal

The absorption of bile components by the wall of the gallbladder can be detected in various ways (a) by the presence of bile components in the efferent veins and lymphatic vessels of the gallbladder and (b) by variations in the composition of the bile inside the gallbladder

The collection of blood or lymph flowing from the gallbladder is a difficult feat, hence, the second method of study was used

Method of Collecting Bile—Dogs anesthetized with a compound of chloral and dextrose were employed in this study The animal was tied in dorsal decubitus on the operating table A medial abdominal incision, as large as possible, was made and was extended to the right at its upper end This last incision was made

9 Riegel, C, Johnston, C G, and Ravdin, I S Studies on Gall Bladder Function VIII The Fate of Bile Pigment and Cholesterol in Hepatic Bile Subjected to Gall Bladder Activity, J Exper Med 56 1, 1932

10 Sweet, J E Gall-Bladder Its Past, Present and Future, Internat Clin 1 187, 1924

11 Ravdin, I S, and Morrison, J L Gallbladder Function The Contractile Function of the Gallbladder, Arch Surg 22 810 (May) 1931

at a right angle to the first incision and between clamps so as to avoid hemorrhage. The duodenum was pulled outward gently so as to exteriorize the gallbladder. The portion of the neck of the gallbladder next to the cystic duct was dissected with a blunt instrument to free it from its surroundings. From the neck outward runs a solid whitish band containing vessels. This was dissected away a little so that a ligature could be passed around the neck only. After the ligature was in place the cystic duct was opened a few millimeters with scissors and a urethral catheter was pushed through the incision into the gallbladder. The gallbladder was then emptied, care being taken that the holes of the catheter were in the middle of the gallbladder. The ligature around the neck was then tied securely. The gallbladder was carefully washed out with tepid physiologic solution of sodium chloride until the fluid came away colorless. At times to the washing fluid was added 1 or 2 drops of ammonia water to dissolve any mucus that might be left on the inner wall of the gallbladder. A small amount of bile with a known proportion of pigments was then introduced, and the catheter was closed with a clamp. Meanwhile the abdominal wall was closed, with the catheter left protruding.

After two to eight hours the animal was killed by puncture of the medulla oblongata. The gallbladder was taken out without previous emptying, in order that it might be ascertained that the ligature about the neck was in good condition and that there had been no loss of bile. If it was found that the ligature was not intact, the results were discarded. If the gallbladder was in perfect condition, its content was emptied carefully into a graduated vessel. The gallbladder was opened with scissors, and the bile adherent to the wall was allowed to drip into the container. The total amount of bile was measured. When considered necessary, the gallbladder was washed with saline solution to remove any remaining bile. The aspect of the inner surface of the wall was then examined. If edema was present, the experimental data were considered worthless. For the data to be accepted as reliable, the wall had to be free from hemorrhagic lesions due to the catheterization. Furthermore, the data were accepted as reliable only for those experiments in which half the liquid volume introduced was absorbed. It can readily be understood why a number of the experiments were excluded, in fact, the data for 42 dogs were discarded.

Results—The results obtained have been divided into two main groups with regard to the concentration of pigments. This separation into two groups is purely arbitrary. It can be seen in table 2 that in 13 experiments the values for pigment varied so that the differences ranged from +9.4 to -23.5 per cent, in 7 experiments the diminution was between -10.1 and -23.5 per cent. The average diminution was 10.6 per cent. With bilirubin concentrations of over 200 mg per liter (table 2), the variations were much smaller, they oscillated between +1.5 and -18.7 per cent. Only once in the 10 experiments was the extreme value of -18.7 obtained. The average of the experiments¹ was a diminution of bilirubin of -3.3 per cent, fairly similar to the value given by Riegel, Johnston and Ravdin (-4.8 per cent).

All these results lead to the belief that bilirubin is better absorbed when its concentration is low. However, it does not seem possible to establish a law with regard to the absorption and its regulation by the

concentration of pigment, apparently there is no threshold for the absorption

With the sole purpose of determining whether absorption is greater with low than with high concentrations, some experiments were carried

TABLE 2—*Bilirubin Content of the Bile in the Gallbladder (Concentrations of Less Than Two Hundred Milligrams per Liter)*

Dog No	Weight, Kg	Time Hr Min	Introduced Bile			Removed Bile			Difference	
			Bilirubin			Bilirubin				
			Cc	Mg per Liter	Mg	Cc	Mg per Liter	Mg	Mg	%
1	14.5	6 20	20	85.0	1.70	14.8	87.5	1.30	-0.40	-23.5
44	12.0	8	15	80.0	1.20	5.9	167.5	1.00	-0.20	-16.6
4	12.0	6 55	18	145.0	1.88	6.0	282.5	1.69	-0.19	-10.1
5	16.5	7 20	15	85.0	1.27	9.0	155.5	1.39	+0.12	+9.4
19	15.0	7	13	192.5	2.50	3.0	767.5	2.30	-0.20	-8.0
20	17.4	7 45	20	55.0	1.10	8.5	105.0	0.89	-0.21	-19.0
21	15.5	8	15	40.0	0.60	6.0	92.5	0.55	-0.05	-8.3
39	18.5	6 20	25	57.5	1.44	16.0	85.0	1.36	-0.08	-5.5
42	21.0	7 30	25	25.0	0.62	5.5	92.5	0.51	-0.11	-16.1
46	20.0	7 45	23	30.0	0.69	11.0	60.0	0.66	-0.03	-4.3
50	17.0	6 50	15	52.5	0.78	6.5	92.5	0.60	-0.18	-23.0
52	26.5	6 25	33	37.5	1.23	16.0	50.0	1.32	+0.09	+7.3
57	27.0	7 15	30	42.5	1.27	12.0	85.0	1.02	-0.25	-19.6
Average										-10.6

TABLE 3—*Bilirubin Content of the Bile in the Gallbladder (Concentrations of More Than Two Hundred Milligrams per Liter)*

Dog No	Weight, Kg	Time Hr Min	Introduced Bile			Removed Bile			Difference	
			Bilirubin			Bilirubin				
			Cc	Mg per Liter	Mg	Cc	Mg per Liter	Mg	Mg	%
8	13.5	7 55	15	345.0	5.33	4.4	1,135.0	4.98	-0.35	-6.5
47	18.0	6 30	20	240.0	4.80	12.0	392.5	4.71	-0.09	-18.7
12	19.0	8	18	327.5	5.90	9.2	642.5	5.91	+0.01	+0.01
16	12.5	5 45	13	315.0	4.09	6.4	610.0	3.90	-0.19	-4.6
18	30.0	7 20	22	212.5	4.68	13.1	350.0	4.59	-0.09	-1.9
24	27.0	7	20	372.5	7.45	11.0	687.5	7.56	+0.11	+1.4
27	24.0	7 30	25	407.5	10.18	13.0	792.5	10.29	+0.11	+1.0
31	25.0	8	20	355.0	7.10	9.3	752.5	7.00	-0.10	-1.4
35	16.2	5 45	15	432.5	6.49	7.8	802.5	6.21	-0.28	-4.3
38	19.0	6 10	20	292.5	5.85	10.7	555.0	5.94	+0.09	+1.5
Average										-3.3

out in which the absorption of different concentrations was tested in the same animal. The animal was prepared according to the method previously described, and a definite amount of bile with a known percentage of pigment was introduced. After three or more hours the gallbladder was emptied and washed many times with tepid physiologic solution of sodium chloride until the solution came away clear. The

total amount of bile was studied. Later, bile with a different concentration of pigment was introduced, and the same procedure was carried out. For each animal bile with a concentration of over 200 mg per liter and bile with a concentration of less than 200 mg per liter were

TABLE 4—*Bilirubin Content of the Bile in the Gallbladder* *

Dog No	Weight, Kg	Time Hr Min	Introduced Bile			Removed Bile			Difference	
			Cc	Bilirubin		Cc	Bil rubin,† Mg			
				Mg per Liter	Mg			Mg	%	
62	30.5	{ 2 45	25	37.5	0.94	12.5	0.87	-0.10	-10.5	
		{ 2 45	25	255.0	6.37	15.0	6.27	-0.10	-1.5	
65	28.5	{ 3 5	30	92.5	2.77	14.9	2.69	-0.08	-2.8	
		{ 3 5	30	310.0	9.31	17.5	9.32	+0.01	+0.1	
66	22.5	{ 2 50	20	85.0	1.70	11.6	1.49	-0.21	-12.3	
		{ 2 50	20	355.0	7.10	9.5	7.10	0.00	0.0	
68	27.0	{ 3	35	410.0	14.52	21.7	14.48	-0.04	-0.2	
		{ 3	35	67.5	2.36	24.0	2.25	-0.11	-4.6	
70	23.0	{ 3 15	22	370.0	8.14	14.2	8.17	-0.03	+0.3	
		{ 3 15	22	125.0	2.75	14.6	2.70	-0.05	-1.8	
71	21.5	{ 3 5	20	465.0	9.30	11.5	9.30	0.00	0.0	
		{ 3 5	20	117.5	2.34	13.1	2.25	-0.09	-3.8	

* Two experiments were carried out in each case, different concentrations of bilirubin being used.

† The concentration of the extracted bile could not be established, because of dilution by the washing fluid.

TABLE 5—*Urobilin Content of the Bile in the Gallbladder*

Dog No	Weight, Kg	Time Hr Min	Introduced Bile			Removed Bile			Difference	
			Cc	Urobilin		Cc	Urobilin			
				Mg per Liter	Mg		Mg per Liter	Mg		
									Mg	%
1	14.5	6 20	20	3.68	0.070	14.8	1.98	0.029	-0.041	-58.5
44	12.0	8	15	1.80	0.027	5.9	1.94	0.011	-0.016	-59.2
4	12.0	6 55	13	1.35	0.017	6.0	1.48	0.009	-0.008	-47.0
5	16.5	7 20	15	1.20	0.018	9.0	1.18	0.010	-0.008	-44.0
19	15.0	7	13	2.27	0.029	3.0	3.87	0.011	-0.018	-62.0
20	17.4	7 45	20	1.98	0.039	8.5	2.09	0.017	-0.028	-71.7
21	15.5	8	15	7.64	0.114	6.0	6.66	0.039	-0.075	-65.8
39	18.5	6 20	25	4.88	0.122	16.0	4.08	0.065	-0.057	-46.7
42	21.0	7 30	25	1.42	0.035	5.5	2.09	0.016	-0.019	-54.2
46	20.0	7 45	23	1.73	0.039	11.0	1.98	0.021	-0.018	-48.7
50	17.0	6 50	15	3.21	0.048	6.5	4.58	0.029	-0.019	-39.5
52	26.5	6 25	33	1.53	0.050	16.0	2.57	0.041	-0.009	-12.0
57	27.0	7 15	30	1.33	0.039	12.0	2.20	0.026	-0.013	-33.3
Average										-50.2

employed. The animal was later destroyed, and a special investigation was made to detect any remaining pigment in the gallbladder. Six experiments were carried out, in 3 of them the first bile introduced was of low concentration, and in the other 3 the first bile was of high concentration. From table 4 it can be seen that undoubtedly the

absorption is greater when the concentration of bilirubin is less than 200 mg per liter

EXPERIMENTAL STUDY OF UROBILIN

Many investigators have studied bilirubin, but I know of no one who has studied the absorption of urobilin by the gallbladder

In the aforementioned experiments a dose of urobilin was also given. In some cases when the concentration of urobilin was too low a certain amount of crystallized urobilin was added. Tables 5 and 6 show the results obtained, which prove that there is considerable absorption of urobilin by the gallbladder, with averages of —50.2 and —48.4 per cent, respectively. The values were much higher than those obtained for bilirubin.

TABLE 6—*Urobilin Content of the Bile in the Gallbladder*

Dog No	Weight, Kg	Time		Introduced Bile			Removed Bile			Difference	
				Urobilin			Urobilin				
		Cc	Mg per Liter	Mg	Cc	Mg per Liter	Mg	Mg	%		
8	13.5	7	55	15	4.31	0.064	4.4	6.07	0.027	-0.037	-57.8
47	18.0	6	30	20	3.87	0.077	12.0	4.31	0.051	-0.026	-33.7
12	19.0	8		18	3.36	0.060	9.2	2.85	0.026	-0.034	-56.6
16	12.5	5	45	13	2.57	0.033	6.4	2.75	0.016	-0.017	-51.5
18	30.0	7	20	22	4.58	0.101	13.1	4.31	0.056	-0.045	-44.5
24	27.0	7		20	1.17	0.023	11.0	0.99	0.011	-0.017	-60.7
27	24.0	7	30	25	1.50	0.037	13.0	1.66	0.022	-0.015	-40.5
31	25.0	8		20	0.94	0.018	9.3	1.02	0.008	-0.010	-55.5
35	16.2	5	15	15	1.48	0.022	7.8	1.59	0.012	-0.010	-45.4
38	19.0	6	10	20	1.73	0.034	10.7	1.98	0.021	-0.013	-38.4
Average											-48.4

PATHOLOGIC CONDITIONS STUDIED BY DUODENAL DRAINAGE IN MAN

A study was also made of patients with cholecystitis, either with or without calculi. The results of duodenal drainage in 70 cases were compiled, these included only the cases in which evacuation of the gallbladder was carried out, that is, those in which B bile was obtained. The cases are divided in three groups in accordance with the proportion of pigments in A and B biles.

In the first group of cases the pigments were in normal proportion. In 41 of the 70 cases (table 7) there was no difference with respect to the amount of pigments. The ratio of the coefficient of increase of bilirubin to the coefficient of increase of urobilin was definitely more than 1, it varied between 1.3 and 8.7, with an average of 2.7.

In the second group of cases the variations in the increases of the urobilin and bilirubin were nearly the same for A and B biles. In 17 cases (table 8) the coefficient of pigmentary increase for B bile was

practically the same for bilirubin and urobilin, in other words, the ratio was 1 or almost 1

In the third group the increase of urobilin in B bile was greater than the increase of bilirubin. In 12 cases the coefficient of increase of

TABLE 7—*Normal Proportions of Pigments in Bile of Patients with Lesions of the Biliary Tract*

Case No		Bilirubin			Urobilin			Ratio of
		A Bile, Mg per Liter	B Bile, Mg per Liter	Coefficient of Increase	A Bile, Mg per Liter	B Bile, Mg per Liter	Coefficient of Increase	Bilirubin Increase to Urobilin Increase
26	Nonlithiasic cholecystitis	20.0	115	5.7	0.34	0.81	2.4	2.3
27	Nonlithiasic cholecystitis	18.0	167	9.2	1.89	3.68	1.9	4.8
28	Cholelithiasis	18.0	250	13.8	0.81	6.07	7.5	1.8
29	Nonlithiasic cholecystitis	62.0	81	1.3	1.89	1.53	-0.8	2.5
30	Cholelithiasis	10.0	393	39.3	0.84	12.00	14.3	2.7
31	Nonlithiasic cholecystitis	60.0	145	2.4	6.07	9.65	1.5	1.6
32	Nonlithiasic cholecystitis	18.0	87	3.1	0.34	0.53	1.7	1.8
33	Nonlithiasic cholecystitis	62.0	236	3.8	0.81	0.69	-0.8	4.2
34	Nonlithiasic cholecystitis	100.0	212	2.1	0.85	1.12	1.3	1.6
35	Nonlithiasic cholecystitis	63.7	218	3.4	1.12	2.85	2.5	1.3
36	Nonlithiasic cholecystitis	218.0	406	1.8	1.80	2.49	1.3	1.3
37	Nonlithiasic cholecystitis	22.0	204	9.2	0.58	0.88	1.6	5.7
38	Cholelithiasis	22.0	455	20.6	0.34	3.68	10.8	1.9
39	Nonlithiasic cholecystitis	100.0	450	4.5	1.40	4.88	3.5	1.3
40	Appendicitis, cholecystitis	375.0	755	2.0	1.05	1.40	1.3	1.5
41	Cholecystitis	28.0	200	7.1	0.34	0.64	2.0	3.5
42	Cholecystitis	87.0	262	3.0	1.29	1.89	1.4	2.1
43	Cholecystitis	16.0	100	6.2	0.38	0.69	1.8	3.4
44	Cholelithiasis	10.0	45	4.5	0.59	1.82	3.1	1.4
45	Cholecystitis	35.0	85	2.4	0.97	1.23	1.2	2.0
46	Cholecystitis	72.0	1,000	13.8	0.48	1.85	3.9	3.5
47	Cholelithiasis	57.0	337	5.9	0.81	1.89	2.3	2.5
48	Cholelithiasis	68.0	237	3.4	0.85	2.10	2.4	1.4
49	Cholecystitis	15.0	105	7.0	0.34	1.33	3.9	1.7
50	Cholelithiasis	80.0	670	8.3	1.89	2.10	1.1	7.5
51	Cholecystitis	300.0	750	2.5	9.06	12.04	1.3	1.9
52	Cholelithiasis	22.0	86	3.9	0.47	0.99	2.1	1.8
53	Cholecystitis	13.0	262	20.1	0.46	1.07	2.3	8.7
54	Cholecystitis	83.0	850	10.2	0.99	3.68	3.7	2.7
55	Cholecystitis	20.0	85	4.2	1.11	2.10	1.8	2.3
56	Cholecystitis	110.0	185	1.6	4.08	4.88	1.1	1.4
57	Cholecystitis	15.0	62	4.1	0.81	0.89	1.1	3.7
58	Cholecystitis	55.0	160	2.9	2.57	4.88	1.8	1.5
59	Cholecystitis	25.0	60	2.4	0.81	1.40	1.7	1.4
60	Cholecystitis	10.0	115	11.5	1.76	5.22	2.9	3.9
61	Cholecystitis	50.0	95	1.9	0.34	0.46	1.3	1.4
62	Cholecystitis	30.0	75	2.5	0.81	1.53	1.8	1.3
63	Cholecystitis	35.0	100	2.8	0.69	0.89	1.3	2.1
64	Cholecystitis	20.0	75	3.7	0.81	1.20	1.4	2.6
65	Cholecystitis	21.2	362	17.0	0.38	0.81	2.1	8.1
66	Cholecystitis	62.5	150	2.4	0.81	0.69	-0.8	3.2
Average								2.7

urobilin was larger than that of bilirubin. In these cases the ratio was, of course, less than 1. This value is smaller the larger the increase of urobilin with respect to the increase of bilirubin (table 9)

TABLE 8—Data for Patients with Cholecystitis Who Showed a Similar Concentration of Bilirubin and Urobilin in A and B Biles

Case No	Condition	Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		A Bile, Mg per Liter	B Bile, Mg per Liter	Coefft cent of Increase	A Bile, Mg per Liter	B Bile, Mg per Liter	Coefft cent of Increase	
67	Cholelithiasis	137.0	175	1.3	1.87	2.49	1.3	1.0
68	Cholecystitis	63.0	103	1.5	1.66	2.49	1.5	1.0
69	Cirrhotic jaundice	38.0	68	1.7	0.46	0.82	1.7	1.0
70	Cholecystitis	62.0	102	1.6	1.69	2.96	1.7	0.94
71	Cholecystitis	259.0	891	3.4	0.90	3.21	3.5	0.97
72	Cholecystitis	93.0	193	2.1	0.46	0.99	2.1	1.0
73	Cholecystitis	40.0	135	3.4	0.94	3.36	3.5	0.97
74	Nonlithiasic cholecystitis	72.0	400	5.5	1.29	6.66	5.1	1.07
75	Nonlithiasic cholecystitis	53.0	115	2.1	0.81	1.53	1.9	1.10
76	Nonlithiasic cholecystitis	15.0	75	5.0	0.34	1.53	4.5	1.11
77	Cholecystitis	12.0	120	10.0	0.51	4.83	9.5	1.04
78	Cholelithiasis	50.0	141	2.8	0.69	2.10	3.0	0.92
79	Nonlithiasic cholecystitis	21.0	56	2.6	0.34	0.89	2.8	0.93
80	Nonlithiasic cholecystitis	125.0	340	2.7	1.25	3.63	2.9	0.93
81	Angiocholecystitis	31.0	87	2.8	0.58	1.69	2.9	0.96
82	Cholecystitis	15.0	45	3.0	0.38	1.29	3.3	0.91
83	Cholelithiasis	12.4	74	5.9	1.53	8.05	5.2	1.13

TABLE 9—Data for Patients with Cholecystitis Who Showed a Greater Increase of Urobilin over Bilirubin in B Bile Than in A Bile

Case No	Condition	Bilirubin			Urobilin			Ratio of Bilirubin Increase to Urobilin Increase
		A Bile, Mg per Liter	B Bile, Mg per Liter	Coefft cent of Increase	A Bile, Mg per Liter	B Bile, Mg per Liter	Coefft cent of Increase	
84	Nonlithiasic cholecystitis	15	32.0	2.1	0.58	1.76	3.0	0.7
85	Nonlithiasic cholecystitis	22	65.0	2.9	0.58	2.49	4.2	0.67
86	Nonlithiasic cholecystitis	60	90.0	1.5	0.81	3.68	4.5	0.3
87	Cholecystitis, pericholecystitis	15	32.0	2.1	0.34	0.82	2.4	0.8
88	Nonlithiasic cholecystitis	38	156.0	4.1	1.29	6.07	4.7	0.8
89	Cholelithiasis	32	120.0	3.5	1.12	6.07	5.4	0.6
90	Nonlithiasic cholecystitis	67	137.0	2.0	1.12	4.88	4.3	0.46
91	Nonlithiasic cholecystitis	23	50.0	2.2	0.75	3.68	4.7	0.46
92	Cholelithiasis	30	70.0	2.3	1.12	2.96	2.6	0.88
93	Cholecystitis	74	155.0	2.1	0.94	2.75	2.9	0.72
94	Cholecystitis	65	123.5	1.9	0.46	1.02	2.2	0.86
95	Cholecystitis	65	140.0	2.1	1.05	4.88	4.6	0.47

TABLE 10—Pigments in Bile Obtained After Cholecystectomy

Hours	Bilirubin, Mg per Cc	Urobilin, Mg per Cc	Ratio of Bilirubin to Urobilin
9	2.4	0.005	450
11	1.2	0.0008	1,500
13	1.2	0.0006	2,000
15	1.1	0.00072	1,666
17	1.2	0.00066	1,818
20	0.9	0.0009	1,000
7	0.8	0.00072	1,111
9	1.1	0.00062	1,835

TABLE 11—Concentration of Urobilin and Bilirubin When Cecal Material Was Introduced into the Gallbladder

Dog No	Weight, Kg	Time Hr Min	Bilirubin			Urobilin		
			Introduced, Mg	Removed, Mg	Difference, %	Introduced, Mg	Removed, Mg	Difference, %
74	12.8	3 40	1.88	1.69	-10.1	0.18	0.29	+61.1
76	15.5	4 10	4.09	3.68	-10.0	0.23	0.34	+21.4
77	14.0	2 55	3.90	3.64	-6.6	0.37	0.46	+24.3
79	14.5	3 45	1.27	1.12	-11.0	0.22	0.31	+40.9
80	16.0	3 55	1.70	1.62	-4.7	0.45	0.61	+35.5

COMMENT

Of the aforementioned groups of cases in which duodenal drainage was carried out, the most interesting was no doubt the third group, in which the concentration of urobilin was increased more than that of bilirubin. As it is known that the absorption through the wall of the gallbladder is higher for urobilin than it is for bilirubin, one is compelled to admit that in order for this to occur there must be local production of urobilin. This production can occur only at the expense of bilirubin, surely in much the same way as stercobilin is formed in the intestine, that is, by bacterial action. It must be remembered that no one has ever demonstrated the formation of urobilin experimentally in the body apart from this bacterial action. Then, in order to accept the theory of local formation of urobilin in the gallbladder, there must be bacteria in the bile. The patients with this type of bile therefore have cholecystitis.

The second group of patients had bile of a type intermediate between the normal and the obviously pathologic. To explain the fact that the increase in the urobilin concentration was equal to the increase in the bilirubin concentration, the theory of local formation of urobilin must again be accepted. The considerable absorption of urobilin by the wall of the gallbladder with respect to that of bilirubin must be compensated for by the formation of the same amount as is absorbed in order that the coefficients of increase may remain the same. Again, one must admit that the bile of these patients contained bacteria, and, as a consequence, the patients had cholecystitis.

In spite of the fact that it was obtained from patients with cholecystitis, the bile obtained in the first group of cases did not differ from normal bile. This can be explained as follows. In the first place, there may be inflammation of the gallbladder without the production of any modification in the bile contained in it. Second, the bile may contain bacteria but not the organisms capable of transforming bilirubin into urobilin. Third, the bile may contain bacteria and may show local production of urobilin, but the amount produced is smaller than the amount absorbed.

Heretofore it has been taken for granted that the ratio of bilirubin to urobilin in bile from the liver is always the same. B bile may be considered to be the result of the mixture of hepatic bile secreted during a fairly long period while A bile represents the secretion of only a short period. As I pointed out in 1933, the relation between the two pigments is not always the same. In a case in which cholecystectomy was performed the results (shown in table 10) indicated a considerable variation in the bilirubin-urobilin ratio. In spite of the great absorption of urobilin by the wall of the gallbladder, however, information derived from study of the pigment is of great importance.

In an attempt to reproduce experimentally the formation of urobilin in the gallbladder, a series of experiments was carried out on dogs with the aforementioned technic. The only difference was that when bile was introduced into the gallbladder, several drops of cecal content was also introduced. The cecal content was obtained from the same animal by puncture of the cecum with a large needle. After several hours the animal was killed, and an examination similar to that already described was made. The results recorded in table 11 show clearly that in these animals a certain amount of urobilin was produced in the gallbladder and that it could have come only from the bilirubin.

SUMMARY

The concentrations of bilirubin and urobilin are higher in B bile than in A bile.

The increase in concentration of urobilin is normally lower than that of the bilirubin. This is due to the fact that only a small amount of bilirubin is absorbed by the wall of the gallbladder, while urobilin is absorbed in surprisingly large amounts.

In a certain number of cases of cholecystitis (41.4 per cent of our cases) the production of urobilin in the gallbladder can be observed. This fact explains why the ratio of increase of bilirubin to increase of urobilin is lower than the normal ratio. Data in this regard can be of use in making a differential diagnosis of inflammation of the gallbladder.

"CARDIAC CIRRHOSIS" OF THE LIVER

A CLINICAL AND PATHOLOGIC STUDY

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The term "cardiac cirrhosis" is used to denote various conditions. According to some authors, the term signifies any type of hepatic fibrosis occurring in a patient with cardiac disease, to others it signifies that the hepatic fibrosis is due to congestive failure, while some authors reserve the application of the term for cases in which cirrhosis of the liver due to congestive failure is responsible for clinical manifestations of portal obstruction, such as recurrent ascites or splenomegaly. Thus, the varied usages of the term imply (1) a simple coexistence of hepatic fibrosis and cardiac disease, (2) a causal interrelation between the two anatomic conditions or (3) a causal morphologic interrelation which results in clinical manifestations of portal obstruction.¹

These different connotations of the term have been responsible in part for the conflicting statements in the literature. There has also been considerable discussion as to the site and nature of the fibrosis in the liver, certain authors have stated that the apparent fibrosis represents only a simple condensation of reticular fibers almost always confined to the centers of the lobules, and other investigators have attributed the changes to active proliferation of fibroblasts. Confronted in certain cases of congestive failure with the question of the presence of cardiac cirrhosis and with a paucity of pertinent available information, we undertook the following investigation of an unselected series

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1 Gerlach, W. Die Kreislaufstörungen der Leber, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol 5, pt 1, p 71. Roessle, R. Entzündungen der Leber, *ibid*, p 243

of consecutive cases in which autopsy was done in order to learn—(1) the incidence of hepatic fibrosis in all cases of congestive heart failure, (2) the types and degrees of hepatic fibrosis in cases of congestive failure of varying duration, (3) the difference between these findings and those in cases in which there is no congestive failure, and (4) the incidence of hepatic fibrosis in cases of congestive failure compared with that in patients with disease of the biliary tract

Such a comparison of the incidence and degrees of the various types of hepatic fibrosis in cardiac and noncardiac pathologic conditions should indicate the significance of congestive failure as a factor in the causation of cirrhosis of the liver

TABLE 1—*Incidence of Fibrosis of the Liver in Two Thousand Unselected Cases*

Type of Fibrosis	Nature of Disease	Degree of Fibrosis			Total No of Cases
		+	++	+++	
Portal*	Chronic passive congestion	29	5	6	40
	Disease of the biliary tract	31	1	6	38
	Both chronic passive congestion and disease of the biliary tract	5	2	1	8
	Neither	80	19	27	126
Central	Chronic passive congestion	13	9	2	24
	Both chronic passive congestion and disease of the biliary tract	1	1	0	2
Combined portal and central	Chronic passive congestion	7	6	1	14
	Disease of the biliary tract	1	0	0	1
	Both chronic passive congestion and disease of the biliary tract	1	1	1	3
Biliary	Disease of the biliary tract	23	10	4	37
	Both chronic passive congestion and disease of the biliary tract	0	2	0	2
Diffuse	Chronic passive congestion	1	0	1	2
	Disease of the biliary tract	0	2	2	4
	Neither	0	2	0	2
					303

* Since slight increases in fibrous tissue in the portal areas cannot be detected with absolute certainty, only those livers with definite degrees of fibrosis in these areas are included

METHODS

Two thousand consecutive autopsy protocols were examined, and the following four groups of cases were selected for further study in order to ascertain the interrelation of chronic passive congestion, hepatic fibrosis and certain other possible factors in the production of an increase of connective tissue in the liver. Cases of chronic passive congestion, cases of disease of the biliary tract, cases in which both conditions were present and cases in which neither condition was present were studied as four separate groups. Patients were considered to have had chronic passive congestion only if definite edema of the dependent parts had been present. Patients were considered to have had disease of the biliary tract if there was postmortem evidence of chronic cholecystitis, cholelithiasis, carcinoma of the ducts, obstructing

carcinoma of the head of the pancreas or of the gallbladder or infection of the biliary tract

The incidence of fibrosis in each of the four groups was ascertained in the following manner. Cases in which, according to the postmortem protocol, there was a definite increase in fibrous tissue were selected for further study. In each instance the microscopic examination was repeated in order to verify the finding of increased fibrous tissue, and if the increase was questionable the case was discarded from this category. For this reason approximately one quarter of the cases in which the presence of periportal fibrosis had been recorded were excluded. Since no case in which the pathologist had not observed increased hepatic fibrosis was included in this group, any error involved in the method would lead to too low rather than too high a percentage. As a final check on the accuracy of the estimates, slides of liver tissue classified as (1) normal and (2) showing increased fibrosis (particularly specimens in which the fibrosis was characterized as 1 plus) were reexamined by another method. At the suggestion of Dr. Monroe Schlesinger a group of such slides was taken, six arbitrary areas were marked, and an observer unacquainted with the classification of the cases estimated the percentage of each field occupied by central and by periportal fibrosis. The results were in accord with those previously recorded.

The microscopic pathologic changes in all cases in which increased hepatic fibrosis was found were classified according to five general types: (1) periportal fibrosis, (2) biliary fibrosis, (3) central fibrosis, (4) patchy or diffuse fibrosis and (5) combined portal and central fibrosis. The term biliary cirrhosis was applied only to specimens showing proliferation of the bile ducts, inflammatory cells and fibrosis about the bile ducts. (Some of the specimens classified as showing periportal fibrosis may conceivably have been representative of the end stage of biliary cirrhosis. They lacked, however, one important criterion for this diagnosis, namely, inflammatory cells.) Each of these types of fibrosis was subdivided into groups according to the degree of pathologic change. Slight degrees of increase in central fibrous tissue signified any fibrosis around the central vein which clearly could not be ascribed to condensation of the reticulum. For practically all the specimens aniline blue connective tissue stain was used, and if this disclosed collagen fibrils pathologic fibrosis was considered to be present. Because of the normal variation in the amount of periportal connective tissue, particularly the increase usually found in old persons, only instances in which the increase was unquestionable were included. In any given case the degree of increase represents the average finding in several slides; in some fields the increase in fibrous tissue was less than the average, in others, it was greater. The same considerations apply to specimens classified as showing 2 plus or 3 plus fibrosis. The 3 plus

group included specimens in which more than half of the parenchyma was replaced by fibrous tissue and the liver showed gross pathologic change, such as hobnailed surface, atrophy or the appearance of *hepar lobatum*. Of the specimens showing periportal involvement, 40 showed advanced portal, or Laennec's, cirrhosis. The group designated as 2 plus showed intermediate degrees of increase in either central or periportal fibrosis, the connective tissue extended out into the parenchyma of the lobules.

RESULTS

The ages of all patients with increase in the various types of fibrosis was ascertained, it was found that the fibrosis could not be

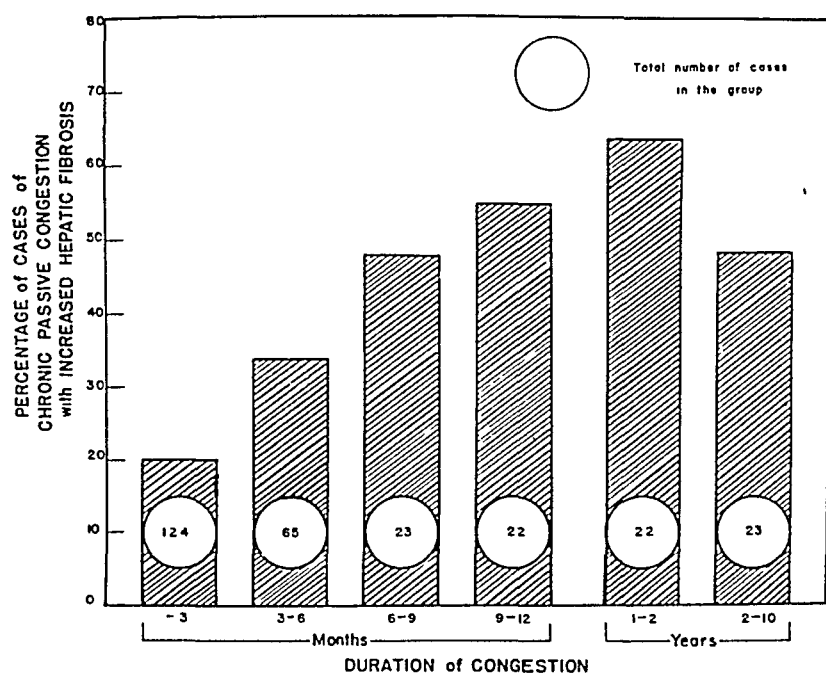


Fig 1—Relation between the duration of congestive failure and the incidence of increased hepatic fibrosis. It is shown that the longer the duration of congestive failure, the higher the incidence of increased hepatic fibrosis.

attributed to the aging process. Of the 2,000 cases there was unquestionable increase of connective tissue in the liver in 303, or 15 per cent, the average age of the patients in this group was 56 years.

1 The first group consisted of cases in which a diagnosis of chronic congestive heart failure was made ante mortem. Of the 2,000 cases, 286, or 14.3 per cent, were in this group. The average age of the 286 patients at death was 50.3 years, as compared with the average of 50.5 years for the entire group. The duration of heart failure, ascertained as accurately as possible from the clinical histories, was divided into several periods, and the number of cases in each period was plotted (fig 1). Of the 286 cases of chronic passive congestion,

increased hepatic fibrous tissue was found in 95, or 33 per cent (table 2). A study was made of this group of 95 cases to ascertain the following facts (1) the type and degree of fibrosis (table 2), (2) the relation between the incidence of fibrosis and the duration of congestive failure (fig 1), (3) the relation between the degree of fibrosis and the duration of congestive failure (fig 2), and (4) the incidence of ascites, anemia and jaundice (table 3)

TABLE 2—*Types and Degrees of Pathologic Increase of Connective Tissue in the Liver in Two Hundred and Eighty-Six Cases of Chronic Congestive Heart Failure*

Type of Fibrosis	Degree of Fibrosis			Total No of Cases
	+	++	+++	
Portal	34	7	7*	48
Central	14	10	2	26
Combined portal and central	8	7	2	17
Biliary	0	2	0	2
Diffuse	1	0	1	2
				95

* The appearance of the liver in these 7 cases of extreme portal fibrosis was typical of that seen in Laennec's cirrhosis

TABLE 3—*Comparison of Incidence of Ascites, Jaundice and Anemia in All Cases of Chronic Passive Congestion with That in Cases of Chronic Passive Congestion Plus Hepatic Fibrosis*

	A Cases of Chronic Passive Congestion Plus Hepatic Fibrosis, Percentage	B All Cases of Chronic Passive Congestion, Percentage
Ascites*	59	50
Jaundice	20	16
Anemia†	14	18

* Ascites was considered present when 50 cc or more of fluid was found in the peritoneal cavity at postmortem examination

† Anemia was considered present when the red blood cell count was less than 4,000,000 per cubic millimeter or the hemoglobin value was 60 per cent or less

It was apparent that the incidence of fibrosis was higher in cases of chronic passive congestion than in the entire unselected series, consequently it became of interest to ascertain whether minimal changes in the liver were largely responsible for this difference. As is shown in figure 3, the distribution of the various degrees of fibrosis was approximately the same. The presence or absence of anemia, jaundice or ascites was ascertained in the 286 cases of chronic passive congestion in order to learn the frequency with which these signs were present (table 3)

2 The second group consisted of cases in which there was postmortem evidence of disease of the biliary tract. Three hundred and eighty-

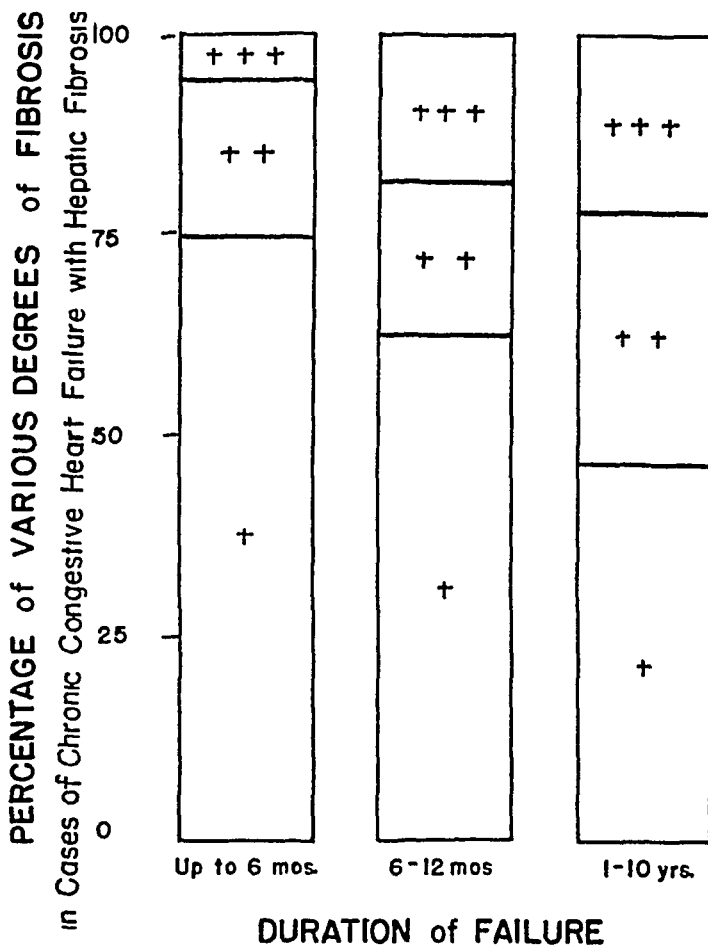


Fig 2—Relation between the incidence of the various grades of cirrhosis and the duration of congestive failure. It is shown that the longer the duration of congestive failure, the greater the proportion of the more severe grades of cirrhosis.

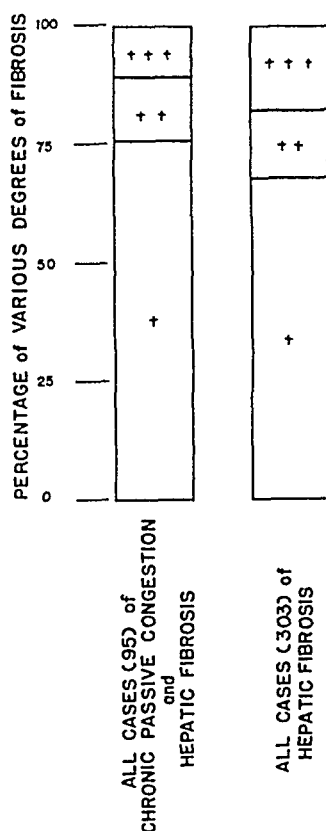


Fig 3—Incidence of various degrees of fibrosis. It is shown that the increased incidence of hepatic fibrosis in cases of congestive failure is not due to a preponderance of minimal degrees of fibrosis.

seven cases, or 19.4 per cent of the 2,000, were in this category, the average age of the patients in this group at the time of death was 60 years. In 95 cases there was a definite increase in connective tissue, the incidence of increased fibrosis was 24 per cent.

3 The third group consisted of cases in which increased hepatic fibrosis was found in the absence of both chronic passive congestion and disease of the biliary tract. One hundred and twenty-eight cases were in this category.

From the foregoing data, the extent to which fibrosis of the liver could be correlated with chronic passive congestion of the heart and also with disease of the biliary tract was ascertained. The incidence of increased hepatic fibrosis in the cases of chronic passive congestion was 33 per cent, as compared with an incidence of 12 per cent in the 1,714 cases in which congestive failure was absent. The difference between the two incidences of 33 per cent and 12 per cent is 21 per cent, and the standard error of this difference is 2.9, the difference is therefore convincing. In 15 cases in which fibrosis was found, pathologic conditions of the biliary tract and chronic passive congestion coexisted. It might be argued that the pathologic condition of the biliary tract was responsible for fibrosis of the liver in these cases and for the high incidence of fibrosis in the cases of chronic passive congestion. If, however, these 15 cases are excluded, hepatic fibrosis which could not be ascribed to disease of the biliary tract was found in 28 per cent of the remaining cases of chronic passive congestion, an incidence almost equally significant.

COMMENT

Of the 286 cases in which death was due to congestive heart failure, increased hepatic fibrous tissue was found in one third, which was approximately three times the incidence found in the remaining 1,714 cases in which congestive failure was absent. The incidence of the various degrees of fibrosis was, in general, similar in both groups of cases (fig. 3). Further, the incidence of fibrosis in cases of chronic passive congestion increased with the duration of congestive failure, and the more severe grades were found in cases in which the illness was of longest duration. Thus, the causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure (figs. 1 and 2). The only type of increase of fibrous tissue peculiar to this group of cases of cardiac decompensation was central fibrosis, for, with a single exception, no instance of central fibrosis was found among the 1,714 cases in which autopsy failed to disclose congestive failure.

It should be noted that other types of fibrosis were also observed in the cases of chronic passive congestion. Indeed, the incidence of each of the various kinds of fibrosis (except biliary fibrosis) was higher in the cases of congestive failure than in the remaining 1,714. Of particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with 9 per cent of the 1,714 cases in which chronic passive congestion was absent. The occurrence of only 2 instances of biliary cirrhosis in the entire group of cases of chronic passive congestion indicates the absence of any etiologic relation between these two conditions, 2 cases being within the expected incidence in 95 random autopsies.

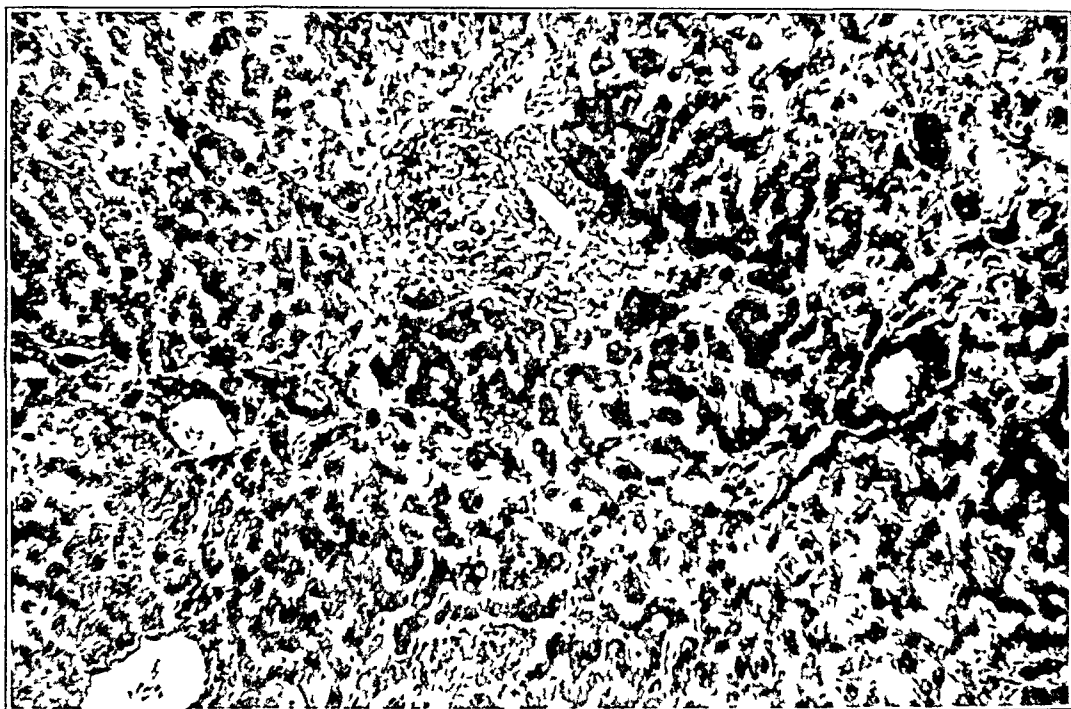


Fig 4—Photomicrograph of a section of the liver. Just above the center is shown an enlarged portal space, with a definite increase in fibrous tissue, some round cell infiltration and extensions of fibrous tissue into the liver substance. At the lower edge of the center there is another portal space with no fibrotic increase. Two central veins may be seen, one on either side, each surrounded by a small, dense ring of fibrous tissue. A third central vein, at the lower left corner, shows a thin ring of fibrosis, which stands out with the aniline blue stain. At the time of death there was no necrosis about the central veins. This condition was tabulated as portal fibrosis 1 plus, central fibrosis 1 plus.

Since it is commonly accepted that disease of the biliary tract is an important cause of hepatic fibrosis, it was of interest to learn that congestive failure is of comparable etiologic significance.

In addition to the 48 cases of congestive failure in which there was only portal fibrosis and the 26 cases in which there was only central

fibrosis, central and portal fibrosis coexisted in 18 instances and were associated with congestive heart failure in all but a single case. This suggests that chronic passive congestion, with resulting anoxemia, may increase the susceptibility of the hepatic tissue to injury in the portal as well as in the central area. In the process of classification, when the increase in portal connective tissue was questionable or when the fibrosis was confined to one area in the liver, the specimen was not classified as showing portal fibrosis. The incidence of portal fibrosis in this series is therefore of increased significance. In 7 cases the severe form of portal cirrhosis, or Laennec's cirrhosis, was present. That more

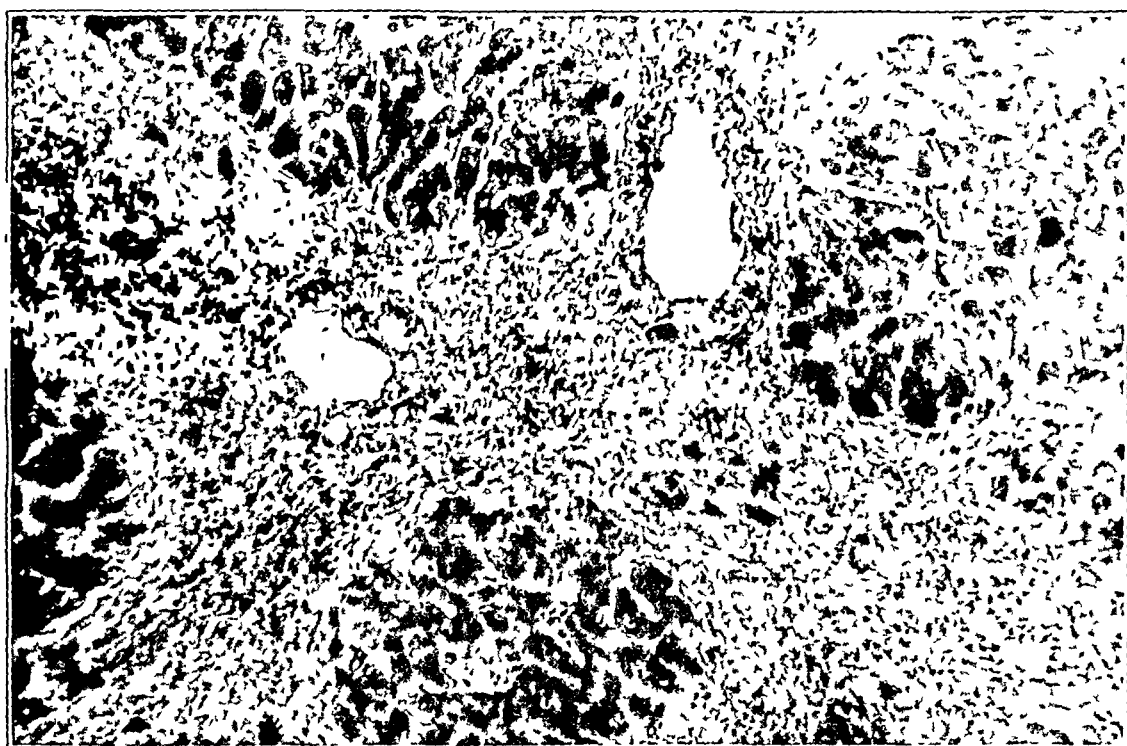


Fig 5—Photomicrograph of a section of the liver. Two dilated central veins are seen, with destruction of liver cells and hemorrhage extending from one to another. There is a ring of dense fibrous tissue about each of the central veins, clearly demarcated by the aniline blue stain. Two normal portal spaces are seen, one in the center on the bottom of the photograph, the other to the right of the larger central vein. Loss of liver parenchyma is marked in central areas, and there is a sharp separation from the relatively unaffected portal areas. The condition was tabulated as central fibrosis 3 plus.

instances of this advanced form were not found may well be due to the relatively short duration of life once congestive failure of severe enough degree to cause hepatic damage has occurred. The characteristics of portal cirrhosis in cases of congestive failure are not peculiar

Our findings are in accord with those of Piéry,² who concluded that stasis of blood predisposes the liver to cirrhosis by the action of toxins and inflammatory processes. The work of Bolton³ is of interest in this connection. He produced passive venous congestion of the liver experimentally and observed not only widespread degeneration of the liver cells about the central hepatic veins, but an "inflammatory infiltration of the portal canals leading to some degree of cirrhosis." Lambert and Allison,⁴ however, concluded that chronic passive congestion never leads to the development of cirrhosis of the usual portal or nodular type. They found an active new growth of connective tissue in only 2 of 112

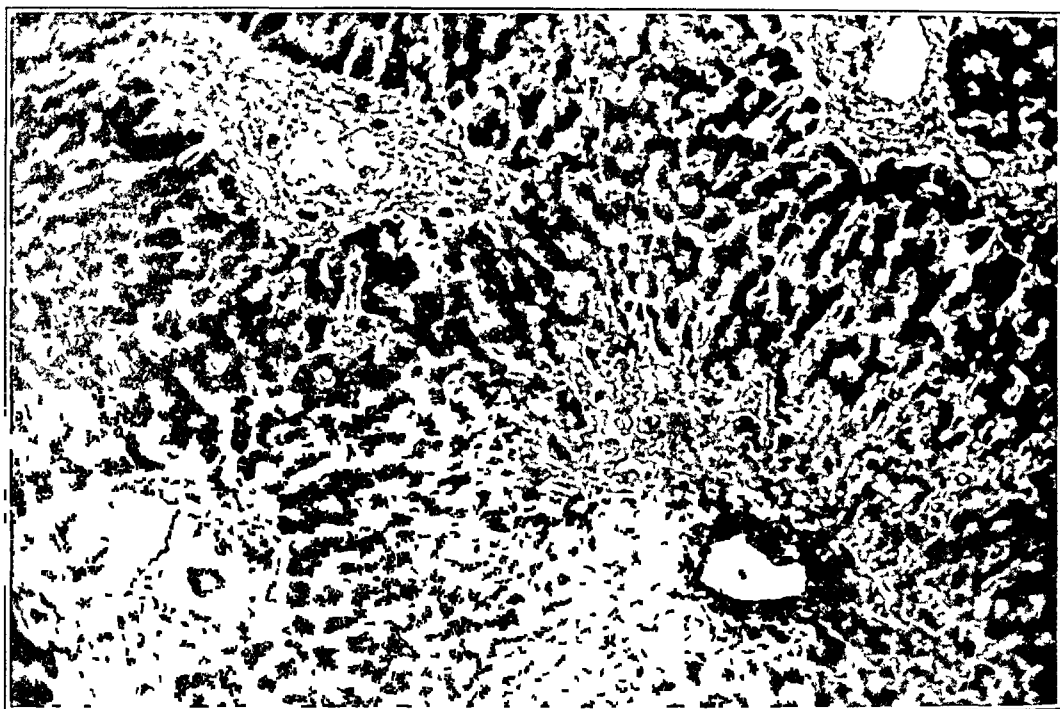


Fig 6—Photomicrograph of a section of the liver. There are three portal spaces, one in each upper corner and one in the lower left corner. These show a definite increase in fibrous tissue, with proliferation of the bile ducts and extensions of connective tissue into the surrounding parenchyma. The central vein in the right lower corner is surrounded by a ring of connective tissue, with fibrils extending out into the liver parenchyma. Areas of congestion and hemorrhage are not sharply outlined. This condition was classified as portal fibrosis 2 plus, central fibrosis 2 plus.

2 Piéry, M. Pathogenie de la cirrhose cardiaque. Stase sanguine et sclérose du foie, étude clinique et anatomopathologique, *Arch gen de med* 4 582 and 714, 1900.

3 Bolton, C. The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, *J Path & Bact* 19 258, 1914.

4 Lambert, R. A., and Allison, B. R. Types of Lesions in Chronic Passive Congestion of the Liver, *Bull Johns Hopkins Hosp* 27 350 (Dec) 1916.

cases of chronic passive congestion, in these 2 only the central portions of the lobules were involved

Central cirrhosis results from the growth of fibrous tissue about the central vein, due to organization of hemorrhage or to metabolic changes occurring as a result of repeated or prolonged anoxemia⁵ Simple condensation of the reticulum about the central vein is not included in this diagnosis In some instances in our series the central fibrosis extended from one central area to another, demarcating the portal lobules, in others it extended irregularly toward the periphery and resulted in an irregular scar These changes have been clearly reproduced experimentally by Zimmerman and Hillsman⁶ Moschcowitz⁷ has suggested that the increase in fibrosis in the central areas may be secondary to sclerosis of the central veins due to marked hepatic venous congestion

In 8 cases the condition was designated "patchy or diffuse fibrosis" (table 1) In only 2 of these was there chronic passive congestion Emboli, as well as bacterial endocarditis⁸ and other conditions, are recognized as a cause of this type of fibrosis⁸ Advanced patchy fibrosis is, however, usually a result of acute yellow atrophy or of syphilis, as in *hepat lobatum*

Clinical cardiac cirrhosis signifying extreme fibrosis which clearly results from chronic passive congestion and which causes evidences of portal obstruction does occur, but is rare Of the 286 cases of congestive failure, there were only 15 in which there was marked (not necessarily predominant) ascites requiring abdominal paracentesis In 6 of these 15 cases cirrhosis of the type caused only by chronic passive congestion, namely, central fibrosis, was demonstrable at autopsy Although increased fibrous tissue was found in the majority of cases in which heart failure has existed for nine months or more, preponderant ascites was not necessarily present The association of anemia or jaundice with congestive failure was not closely correlated with the pathologic increase of connective tissue observed at autopsy, these factors are consequently of no value in diagnosing hepatic cirrhosis clinically Morphologic evidence of increased fibrosis of the liver was seen in all of the 6

5 Rich, A R The Pathogenesis of the Forms of Jaundice, *Bull Johns Hopkins Hosp* 47 338 (Dec) 1930

6 Zimmerman, H M, and Hillsman, J A Chronic Passive Congestion of the Liver An Experimental Study, *Arch Path* 9 1154 (June) 1930

7 Moschcowitz, E Phleboscrosis of the Hepatic Veins as Associated with Chronic Passive Congestion of the Liver and Cardiac Cirrhosis Preliminary Report, in *Contributions to the Medical Sciences in Honor of Dr Emanuel Libman*, New York, International Press, 1932, vol 2, p 857

8 Mallory, F B Cirrhosis of Liver (Shattuck Lecture), *New England J Med* 206 1231 (June 16) 1932

cases in which recurrent ascites was present and heart failure had existed for two years or more

From these studies it would seem that cardiac cirrhosis signifying morphologic increase in connective tissue in the liver consequent to congestive failure is present in approximately 50 per cent of all patients who have had congestive failure nine months or more. While central cirrhosis is characteristic of congestive failure and does not occur in patients with disease of the biliary tract, it would appear that other portions of the liver are also more susceptible to injury in patients with chronic passive congestion. Thus, 48 instances of uncomplicated periportal fibrosis were encountered in the group of 286 cases of chronic passive congestion, which contrasts with an expectancy of only 26 cases if congestive failure were not a contributory factor. The occurrence of 22 additional cases in which there was definitely increased fibrosis of both the central and the portal areas is further evidence of an increased susceptibility of the portal areas to injury under such circumstances.

Excluding the cases in which there was increased connective tissue in both the central and the portal areas, the incidence of portal fibrosis in the 286 cases of congestive failure was 17 per cent, as compared with an incidence of central fibrosis of 9 per cent. The significance of alcoholism⁹ as a contributory factor could not be accurately appraised, although increased consumption of alcohol was not apparent in the records of the patients with congestive failure.

By the foregoing evidence the meaning of the term cardiac cirrhosis is clarified. In the morphologic sense of increased fibrosis being due to chronic passive congestion, one may state that the livers of the majority of patients who have suffered from even mild congestive failure for nine months or more show increased fibrosis, central or portal or both.

The determination of whether cardiac cirrhosis in the clinical sense of increased fibrosis causing clinical manifestations is present must be based on clinical evidence. If there is preponderant ascites, if there is marked elevation of the venous pressure but the liver is not palpable and particularly if the spleen is palpable, clinical cardiac cirrhosis may be assumed to exist. The reverse situation, however, was more frequently present in our series of cases. The liver was enlarged and ascites was present. In such cases, though increased fibrous tissue was present and the surface of the liver generally was nontender and sometimes somewhat irregular, the dilatation of the sinusoids led to an increase in the size of the liver. The liver of a patient with a condition clinically diagnosed as cardiac cirrhosis may show portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

⁹ Moon, V. H. Experimental Cirrhosis in Relation to Human Cirrhosis, *Arch Path* 18: 381 (Sept) 1934.

SUMMARY

An investigation of an unselected series of 2,000 consecutive cases in which autopsy was performed was undertaken in order to learn the incidence, types and degrees of hepatic fibrosis in cases of congestive failure and to make a comparison of these findings with those in cases in which congestive failure was absent

Of the 286 cases of chronic passive congestion, there was an increase of hepatic fibrous tissue in 95, or 33 per cent. In 1,714 cases in which chronic passive congestion was absent the incidence of hepatic fibrosis was 12 per cent. The causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure. The incidence of each of the various kinds of fibrosis except biliary fibrosis was higher in 286 cases of congestive failure than in the remaining 1,714. The only type of increase in connective tissue peculiar to the cases of cardiac decompensation was central fibrosis, for, with a single exception, no instance of central fibrosis was found in 1,714 cases in which autopsy disclosed an absence of congestive failure. Of particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with an incidence of 9 per cent in the 1,714 cases in which chronic passive congestion was not present. While central fibrosis was found only in cases of chronic passive congestion, portal fibrosis also was found in a larger percentage of such cases than in cases in which chronic passive congestion was absent. This suggests that chronic passive congestion with resulting anoxemia, by increasing the susceptibility of the hepatic tissue, is also a contributing factor to fibrosis in the portal areas.

By the evidence obtained in this investigation the meaning of the term "cardiac cirrhosis" is clarified. Cardiac cirrhosis signifying morphologic increase in connective tissue in the liver consequent to congestive failure is present in the majority of patients who have suffered from even mild congestive failure for nine months or more, the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, signifying extreme fibrosis which clearly results from chronic passive congestion and which causes evidences of portal obstruction, does occur, but is rare. Of the 286 cases of congestive failure, there were only 15 in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure, and particularly the presence of a palpable spleen. Not infrequently, however, the liver may be enlarged. In such cases, although increased fibrous tissue is present and

the surface of the liver is generally nontender and sometimes somewhat irregular, the dilatation of the sinusoids leads to an increase in the size of the liver. In a patient in whose case a clinical diagnosis of cardiac cirrhosis has been made, one may find portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

Dr Henry A. Christian made it possible for us to use the records of the Peter Bent Brigham Hospital. Dr Monroe J. Schlesinger cooperated in the study of the pathologic material.

HEMATOLOGY OF STERNAL MARROW AND VENOUS BLOOD OF PREGNANT AND OF NONPREGNANT WOMEN

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AND

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The study of marrow obtained by sternal puncture has been in use at the Vancouver General Hospital since the appearance of the paper by Young and Osgood,¹ and the method has proved of great value. Recently, however, the problem of interpretation of the picture presented by the marrow of pregnant women was raised when marrow was obtained for study from a woman aged 24 years, four months pregnant, with acute lead poisoning. Search of the literature failed to reveal any figures for the sternal marrow of healthy pregnant women, and most of the figures available for healthy persons were based on studies of men only.

The studies herein reported were undertaken with the object of providing normal standards for these groups.

MATERIAL AND METHODS OF THE VANCOUVER GENERAL HOSPITAL

Subjects—Forty pregnant women attending the outpatient maternity clinic of the Vancouver General Hospital were studied. None of these women had a past history suggesting a blood dyscrasia, and all of them were found by consideration of the history and by physical examination at the clinic to be in good health. For comparison, studies were made on 24 healthy nonpregnant women of about the same age. Nurses, technicians and others on the hospital staff volunteered for this purpose. All of those selected felt themselves to be perfectly well at the time of examination, and most of them were found to be healthy according to the history and the results of physical examination. The average age of the pregnant women was 24 years (range 17 to 34 years), and that of the nonpregnant women, 27 years (range 19 to 34 years).

Methods—All methods used were those recommended by Osgood in his "Textbook of Laboratory Diagnosis"² and in the "Atlas of Hematology" by Osgood and Ashworth.³

From the Vancouver General Hospital

1 Young, R H, and Osgood, E E. Sternal Marrow Aspirated During Life. Cytology in Health and in Disease, Arch Int Med 55 186 (Feb) 1935

2 Osgood, E E. A Textbook of Laboratory Diagnosis, ed 2, Philadelphia, P Blakiston's Son & Co, 1935

3 Osgood, E E, and Ashworth, C M. Atlas of Hematology, San Francisco, J W Stacey, Inc, 1937

By sternal puncture (Osgood and Ashworth,³ page 205) 10 cc of marrow was obtained. This was introduced into a tube containing 2 mg of oxalate (Osgood,² page 393) per cubic centimeter. Ten cubic centimeters of blood was obtained by venipuncture and introduced into oxalate. On each specimen of marrow, erythrocyte and total nucleated cell counts, hemoglobin estimation, a differential cell count of 500 cells in a smear stained with Wright's stain, a reticulocyte count and determination of the sedimentation rate were performed. On the blood the same procedures were used except that only 200 cells were counted in the differential counts. All of the laboratory studies were made by one of us (E. A. P.) with research care.

The erythrocyte, leukocyte and total nucleated cell counts were done in duplicate with pipets calibrated by the Bureau of Standards with meticulous attention to detail (Osgood,² page 404). The hemoglobin estimations were made by the Haskins-Sahli method (Osgood,² page 396). The results are reported both in grams and in percentage of the normal hemoglobin coefficient for women (Osgood,² page 420). The sedimentation rates were determined by the modified Westergren method (Osgood,² page 431) for use with oxalated blood. Reticulocyte counts were made by the Osgood and Wilhelm method (Osgood and Ashworth,³ page 206). Before the differential counts were made the slides were surveyed under lower magnification (Osgood and Ashworth,³ page 143) to select areas for counting where the erythrocytes did not touch each other and where the leukocytes were evenly distributed. If the counts from different slides did not check within reasonable limits, 300, and in rare instances 500, additional cells were counted on the marrow smears. The nomenclature and the criteria of cell identification and classification are those given in tabular form and illustrated in the "Atlas of Hematology" by Osgood and Ashworth.³

RESULTS

The results of these studies are given in tables 1 to 11.

Limitation of space makes it necessary to exclude from the tables such cells as proplasmacytes (Turk cells), plasmacytes, basophilic granulocytes (myelocytes) and eosinophilic and basophilic progranulocytes (promyelocytes), which were all present in numbers less than 0.1 per cent. For reasons of economy, also, eosinophilic metagranulocytes (metamyelocytes) were included with the eosinophilic granulocytes and the mature eosinophils with the eosinophilic rhabdocytes (staff cells).

COMMENT

It should be noted (tables 2 and 6), as Dieckmann and Wegner⁴ have shown, that the erythrocyte counts and hemoglobin estimations for pregnant women are 10 to 15 per cent lower than for healthy nonpregnant women of the same age group. The erythrocyte and hemoglobin values for healthy nonpregnant women (tables 4 and 6) are somewhat lower than those reported by others⁵ for healthy women of this age group, but the series investigated was small. The hemoglobin and

4 Dieckmann, W. J., and Wegner, C. R. The Blood in Normal Pregnancy I. Blood and Plasma Volumes, *Arch Int Med* **53** 71 (Jan) 1934, Studies of the Blood in Normal Pregnancy II. Hemoglobin, Hematocrit and Erythrocyte Determinations and Total Amount of Variations of Each, *ibid* **53** 188 (Feb) 1934.

5 Osgood, E. E. Normal Hematologic Standards, *Arch Int Med* **56** 849 (Nov) 1935.

TABLE 1—Values for Sternal Marrow of Healthy Pregnant Women

Case Number	Age	Lymphocytes per Cu Mm	Color Index	Hemoglobin, %	Hemoglobin, Gm	Sedimentation, 15 and 45 Minute Readings	Reticulocytes, %	Total Nucleated Cell Count per Cu Mm	Granuloblasts, % (Myeloblasts)	Progranulocytes Type A, % (Promyelocytes Type A)	Progranulocytes Type S, % (Promyelocytes Type S)	Eosinophilic Granulocytes, % (Eosinophilic Myelocytes)	Neutrophilic Granulocytes, % (Neutrophilic Myelocytes)	Metarubricytes, % (Metarubricytes)	Rhabdomyocytes, % (Unsegmented Polymorphonuclears)	Lobocytes, % (Segmented Polymorphonuclears)	Lymphoblasts, %	Lymphocytes, %	Monocytes, %	Megalo- blasts		Normo- blasts		Disintegrated Cells, %		
																				Karyoblasts, %	Prokaryocytes, %	Karyocytes, %	Metakaryocytes, %			
Trimester 1	01	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	02	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	03	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	04	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	05	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	06	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	07	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	08	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	09	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
	10	3,560,000	1.03	78	11.50	1/1	2.3	11,400	0	1.2	0.2	0.8	1.2	1.8	15.2	37.6	0.6	0.2	28.0	1.0	0.0	0.0	1.8	0.0	3.0	18.0
Trimester 2	11	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	12	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	13	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	14	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	15	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	16	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	17	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	18	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	19	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
	20	3,300,000	1.06	71	10.22	3/25	1.4	50,000	0.5	0.7	0.5	0.2	1.0	4.0	43.5	10.0	0.2	11.0	1.0	0.2	1.0	0.0	0.0	0.0	0.0	16.0
Trimester 3	21	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	22	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	23	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	24	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	25	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	26	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	27	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	28	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	29	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0
	30	3,200,000	1.03	79	10.41	8/11	5.9	30,000	0.1	1.0	1.0	1.0	0.9	0.8	47.6	8.0	1.1	0.1	0.3	0.3	0.3	0.0	0.0	0.0	0.0	0.0

TABLE 2—Values for Blood* of Healthy Pregnant Women

	Case Number	Erythrocytes per Cu Mm	Color Index	Hemoglobin, %	Hemoglobin, Gm	Sedimentation, 15 and 45 Minute Readings	Reticulocytes %	Leukocytes per Cu Mm	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils %	Disintegrated Cells, %
Tri mester 1	1	4,130,000	1 00	82	11 73	Not done		9 800		Normal range				
	2	3,000,000	1 02	64	9 15	Not done		9,600		Normal range				
	3	4,400,000	0 93	82	11 60	4/25	2 6	12,100	74	16	1	0	1	8
	4	1,280,000	0 92	76	10 72	2/11	2 4	8 500	57	31	1	5	0	6
	5	3,780,000	1 02	77	11 01	2/8	1 5	9,450	69	21	6	1	1	2
	6	3,710,000	1 04	77	11 04	8/38	2 0	14,500	57	34	0	4	0	5
	7	4,220,000	0 94	79	11 32	1/8	3 0	9,000	65	32	0	0	0	3
	8	4,550,000	0 96	87	12 42	1/8	2 6	12 250	78	16	2	2	0	2
	9	3,900,000	1 06	84	12 01	1/9	2 2	7,750	61	28	3	1	2	5
	10	3,920,000	1 05	82	11 73	1/6	2 0	9,950	66	26	2	1	0	5
Tri mester 2	1	3,700,000	1 02	76	10 90	5/29	Not done	10,000	53	41	Normal range			
	2	3,250,000	1 06	69	9 80	4/16	Not done	9,050		Normal range				
	3													
	4	5,000,000	0 93	93	13 25	1/6	Not done	10,000	64	24	6	3	0	3
	5	4 230,000	0 94	77	11 04	6/31	Not done	8,100	71	12	7	3	0	7
	6	4,460,000	0 90	81	11 59	9/36	Not done	13,700	69	18	0	1	0	7
	7	3,850,000	0 96	73	10 41	2/26	1 8	7 200	67	20	4	5	0	4
	8	3,880,000	1 07	83	11 87	3/21	2 3	11 000	60	40	6	0	0	7
	9	4,350,000	0 90	78	11 18	2/18	1 6	12,070	78	13	1	1	2	4
	10	4,000,000	0 98	79	11 35	1/35	1 0	13,160	77	14	4	2	0	3
	11	4,140,000	1 04	86	12 30	5/33	2 2	11,200	74	19	4	0	1	2
	12	3,380,000	0 89	59	8 42	6/40	2 2	8,700	55	33	1	0	0	11
	13	3,750,000	1 01	76	10 90	7/36	2 0	10,500	78	15	5	0	0	1
	14	3,850,000	1 00	76	10 87	5/26	3 6	13,500	66	29	2	1	0	2
	15	3,720,000	0 93	69	9 80	10/52	1 0	12,850	67	29	1	0	0	5
Tri mester 3	1	3,500,000	0 95	67	9 58	5/29				Not done				
	2	4,020,000	0 90	72	10 30	7/36	Not done	13,100		Normal range				
	3	3,500,000	1 00	70	10 01	5/25	Not done	6,350	72	Normal range				
	4	4,200,000	1 02	86	12 30	4/27	Not done	12,200	70	29	1	0	0	0
	5	3,450,000	0 97	67	9 58	13/59	Not done	6,800		Normal range				
	6	3,800,000	0 92	70	10 01	15/65	Not done	9,300		Normal range				
	7	3,640,000	0 97	70	10 01	10/34	Not done	7,600		Normal range				
	8	3,800,000	1 01	77	11 01	2/13	Not done	6,800		Normal range				
	9	3,850,000	1 01	78	11 18	12/52	Not done	7,000	65	26	3	3	0	3
	10	3,750 000	1 00	75	10 76	12/45	Not done	7,500	54	38	0	0	1	7
	11	3 310 000	0 94	63	8 97	5/26	Not done	8,950	64	28	2	0	0	6
	12	3 900 000	0 96	75	10 76	2/15	Not done	11 800	62	30	1	2	0	5
	13	4 190 000	0 91	75	10 76	10/40	Not done	7,400	43	48	3	1	1	4
	14	4,266 000	0 77	66	9 38	5/40	1 9	6 900	71	23	4	0	0	2
	15	4,500 000	0 83	75	10 76	2/40	3 4	9,600	78	11	3	1	0	7
	16	4,300,000	1 01	87	12 44	5/23	Not done	11,800	64	29	1	0	1	5

* Peripheral blood was used for the determinations

Les thuyes des par Cu Min

[illegible]

men It is noteworthy that there is no decrease in any of the nucleated erythrocytes during pregnancy (tables 5 and 10), which indicates that the physiologic anemia of pregnancy is due not to decreased erythrocyte production but, as others have shown,⁴ to the increase in plasma volume There is even a slight increase in the reticulocyte counts during pregnancy (tables 2 and 6), suggesting that there may be a slightly increased rate of erythrocyte formation The reticulocyte counts of the blood of healthy nonpregnant women (tables 4 and 6) agree well with those

TABLE 6—*Comparison of the Average, Maximum and Minimum Values for Blood* in the Three Trimesters of Pregnancy and for Pregnant and Nonpregnant Women*

		Erythrocytes per Cu Mm	Color Index	Hemoglobin, %	Hemoglobin, Gm	Sedimentation, 15 and 45 Minute Readings	Reticulocytes %	Eucocytes per Cu Mm	Polymorphonuclears %	Lymphocytes, %	Monocytes, %	Eosinophils %	Basophils %	Disintegrated Cells %
Trimester 1														
Maximum	34	4,550,000	1 06	87	12 42	8/38	1 5	14,500	78	34	6	5	2	8
Minimum	17	3,000,000	0 92	64	9 15	1/6	2 0	7,750	57	16	0	0	0	2
Average	24	3,998,000	1 00	79	11 29	2/14	2 4	10,290	66	26	2	2	1	5
Trimester 2														
Maximum	33	5 000,000	1 07	93	13 25	10/52	4 0	13,700	78	49	7	5	2	11
Minimum	17	3,250 000	0 89	59	8 42	1/6	1 0	7,200	53	12	0	0	0	1
Average	23	3,970,000	0 97	77	10 98	5/29	2 3	10,800	68	24	3	1	0 5	5
Trimester 3														
Maximum	33	4,500,000	1 02	87	12 44	15/65		13,100	78	48	4	3	1	7
Minimum	19	3 310,000	0 77	63	8 97	2/13		6,350	43	11	0	0	0	0
Average	25	3,870,000	0 94	73	10 48	7/36		8,800	64	29	2	1	0 3	4
Pregnant women														
Maximum	34	5,000,000	1 07	93	13 25	16/65	4 5	14,500	78	49	7	5	2	11
Minimum	17	3,000 000	0 77	59	8 42	1/6	1 0	6,300	43	11	0	0	0	0
Average	24	3,930,000	0 96	76	10 86	5/29	2 5	9,920	66	26	3	1	0 3	5
Nonpregnant women														
Maximum	34	4 880,000	1 09	99	14 27	6/38	3 0	12,500	76	50	8	6	2	9
Minimum	19	3,900,000	0 85	72	10 35	0/2	0 5	5 000	38	16	1	0	0	0
Average	27	4,390,000	0 97	86	12 26	1/8	1 6	7,600	52	37	4	2	0 5	5

* Peripheral blood was used for the determinations

reported by Osgood and Wilhelm⁷ for a larger series It is evident from the differential (tables 1 and 5) and absolute (tables 7 and 9) counts that the sternal marrow of pregnant women is somewhat hyperplastic as compared to the sternal marrow of healthy nonpregnant women (tables 8 and 9) but that the hyperplasia affects all types of cells about equally, so that the differential counts (tables 5 and 10) are not significantly different from those for healthy nonpregnant women The

TABLE 7—Absolute Numbers of Each Type of Cell per Cubic Millimeter in Sternal Marrow of Pregnant Women

Case Number	Total Nucleated Cell Count per Cu Mm	Megaloblasts										Normoblasts									
		Granuloblasts (Myeloblasts)	Proerythrocytes (Type A)	Proerythrocytes (Type B)	Eosinophilic Granulocytes	Neutrophilic Granulocytes	Metarubricytes (Meta-myelocytes)	Rhabdomyocytes (Unsegmented)	Polymorphonuclears	Lymphocytes (Segmented)	Basophils	Monocytes	Karyoblasts	Prokaryocytes	Karyocytes	Meta-karyocytes	Dysmature Cells				
Trimester 1	1	45,000	900	675	225	3,150	2,250	14,850	4,050	225	0	6,300	450	900	900	2,700	8,100				
	2	40,100	240	400	197	1,600	2,000	18,400	4,200	400	0	4,400	40	840	640	1,800	5,100				
	3	65,700	854	657	197	4,336	5,913	28,251	7,884	657	0	2,956	328	1,314	2,628	1,182	7,884				
	4	19,000	38	114	494	836	1,140	3,610	4,180	1,140	190	2,964	570	38	608	871	2,011				
	5	37,100	0	371	148	3,932	2,819	11,575	4,526	148	148	2,894	965	0	1,187	965	5,490				
	6	46,500	93	279	279	3,431	2,511	15,345	8,835	465	0	5,673	186	0	930	1,953	4,713				
	7	21,000	0	114	96	1,140	1,104	8,160	4,272	48	144	3,168	240	48	192	912	3,696				
	8	19,700	78	0	39	669	906	8,516	6,619	275	197	3,506	197	472	472	288	2,285				
	9	31,400	722	344	275	3,096	2,752	10,664	4,472	206	68	3,852	206	136	894	619	5,848				
	10	11,400	202	28	28	172	259	2,189	5,414	144	28	4,032	144	86	259	28	1,382				
Trimester 2	1	50,000	250	375	125	2,000	2,000	21,750	5,000	125	0	5,500	500	700	1,500	2,000	8,000				
	2	17,500	18	175	18	875	700	5,950	1,575	18	18	2,975	18	175	1,120	1,225	1,872				
	3	25,000	0	150	50	1,800	1,950	5,150	5,050	150	50	3,900	270	500	550	230	4,100				
	4	17,200	69	138	103	998	1,066	4,128	3,130	206	69	1,686	172	0	619	311	3,936				
	5	125,000	1,270	3,500	1,270	13,125	10,250	46,250	11,750	375	125	10,000	250	0	1,875	7,000	11,500				
	6	21,600	86	86	43	1,126	907	8,388	3,283	389	86	3,931	43	13	259	316	1,034				
	7	15,700	0	220	31	659	251	3,077	3,109	283	94	3,925	43	259	1,210	316	1,034				
	8	40,100	80	241	160	2,165	1,624	16,842	8,662	561	61	3,449	612	80	882	612	3,600				
	9	30,750	123	123	123	2,399	1,853	9,471	5,719	185	61	3,383	185	0	677	751	1,735				
	10	48,200	386	675	96	4,242	2,506	18,609	6,073	289	68	4,000	482	0	1,350	2,603	6,911				
	11	33,900	203	203	72	3,797	2,676	12,204	3,729	271	68	4,000	0	203	716	1,124	3,661				
	12	36,000	72	141	72	2,160	2,016	10,872	7,341	216	0	4,320	216	152	1,800	936	1,176				
	13	30,300	0	303	0	1,818	1,879	10,423	4,515	121	0	5,030	121	424	1,451	819	3,272				
	14	90,000	900	900	1,440	7,740	7,740	42,840	7,200	990	90	7,740	270	180	1,800	3,600	5,100				
Trimester 3	1	70,000	700	700	700	6,300	4,900	29,400	4,200	700	70	4,900	70	2,100	1,400	2,100	11,900				
	2	17,000	0	51	51	391	340	5,270	4,270	170	51	3,961	119	0	51	119	1,921				
	3	42,000	12	810	42	1,650	1,890	15,960	5,460	42	0	2,310	210	1,260	1,260	2,730	7,110				
	4	31,000	68	0	34	1,620	2,040	16,130	5,950	34	0	5,100	34	31	630	850	1,870				
	5	22,600	23	181	22	1,010	1,040	9,492	2,079	180	0	2,485	22	0	452	1,040	3,390				
	6	21,100	21	211	21	717	717	9,284	4,110	105	21	2,216	148	105	566	717	1,329				
	7	21,600	0	295	0	1,033	788	7,774	394	216	49	3,788	98	49	1,033	975	5,896				
	8	15,000	0	225	225	1,320	1,800	17,775	8,100	0	0	5,400	0	0	900	2,700	4,900				
	9	28,700	57	114	114	2,736	2,052	7,751	4,332	114	0	3,219	114	0	1,110	2,708	3,762				
	10	20,100	0	163	163	899	1,142	1,937	2,978	326	122	3,168	408	0	408	1,632	3,216				
	11	31,000	136	310	204	1,292	2,040	12,240	6,528	68	0	1,823	476	68	718	1,700	3,921				
	12	43,600	87	434	87	2,170	2,343	13,714	8,680	260	87	1,600	174	174	1,060	2,000	5,612				
	13	30,000	60	300	120	2,230	2,400	11,160	4,080	300	0	3,540	300	120	1,476	1,200	3,180				
	14	16,900	34	169	68	1,559	1,521	4,901	1,115	34	17	1,318	68	17	612	1,284	3,118				
	15	63,500	675	1,420	635	7,937	3,937	11,923	5,270	635	191	1,381	127	3,076	1,978	8,976	8,982				
	16	30,700	183	610	183	1,830	1,139	9,777	5,978	427	183	3,965	732	0	1,978	1,220	2,681				

TABLE 8—Absolute Numbers of Each Type of Cell per Cubic Millimeter in Stenial Marrow of Nonpregnant Women

Case Number	Total Nucleated Cell Count per Cu Mm	Granuloblasts (Myeloblasts)	Progranulocytes Type A	Progranulocytes Type S	Lymphoblastic Granulocytes	Neutrophilic Granulocytes	Metarubriculocytes (Meta-myelocytes)	Rubriculocytes (Unsegmented)	Lobocytes (Segmented)	Lymphoblasts	Basophils	Lymphocytes	Monocytes	Karyoblasts	Prokaryocytes	Karyocytes	Normoblasts	Disseminated Cells
1	12,000	0	12	21	21	168	168	168	2,928	129	72	2,352	0	0	336	744	384	2,148
2	13,300	0	61	61	0	826	393	3,947	2,142	275	31	2,179	398	0	551	1,010	153	2,907
3	36,300	109	218	363	544	2,511	2,650	9,438	4,171	363	36	3,789	363	0	1,270	2,904	1,089	6,534
4	10,700	11	11	13	13	423	423	1,712	2,675	642	10	2,184	312	10	64	257	48	1,541
5	32,600	65	130	301	130	2,608	2,513	6,781	3,977	196	0	6,320	717	0	1,304	1,936	522	4,564
6	22,000	44	132	0	132	880	2,068	5,896	3,103	220	176	3,314	440	22	440	1,936	660	3,300
7	15,300	93	155	16	122	930	817	3,160	1,767	217	77	3,565	217	16	248	775	264	3,410
8	30,600	122	307	245	122	2,203	2,826	8,568	4,771	181	184	3,244	612	122	784	1,714	918	4,162
9	10,300	31	103	31	41	309	309	1,339	3,193	278	51	2,987	360	0	62	134	51	1,081
10	17,900	72	251	107	36	644	1,074	3,294	2,936	179	113	4,189	430	72	430	788	251	2,649
11	8,800	35	83	53	0	282	334	1,091	2,165	106	9	2,675	111	0	106	239	88	1,302
12	16,000	184	736	363	363	3,404	4,321	11,114	7,084	308	92	5,704	368	0	736	1,472	368	5,704
13	29,100	175	463	233	349	2,095	2,212	8,139	3,899	319	29	3,143	407	0	873	1,921	466	4,074
14	21,800	109	174	109	22	937	1,303	3,989	3,161	171	32	5,070	171	0	327	763	240	5,232
15	16,100	0	161	0	32	1,159	869	4,059	2,769	97	32	2,117	32	0	354	966	354	2,737
16	34,800	279	279	209	140	3,001	1,815	10,719	3,630	279	70	5,235	269	70	1,396	1,745	838	4,836
17	45,000	270	630	630	150	4,140	2,700	14,490	6,720	90	0	1,500	630	90	1,350	2,070	810	5,220
18	26,800	159	371	53	212	2,385	1,325	6,519	3,127	533	0	4,028	265	0	1,060	1,184	848	4,028
19	34,600	69	346	293	346	2,254	1,863	11,833	6,297	316	0	3,252	415	69	969	1,730	484	4,083
20	7,550	15	70	0	30	332	377	1,163	1,182	60	15	1,721	106	0	211	453	106	1,752
21	16,700	63	220	126	157	722	785	3,483	2,763	94	0	2,135	188	63	565	1,256	471	2,375
22	27,800	111	334	0	56	3,058	1,946	8,396	3,447	56	167	2,558	222	111	723	1,612	723	4,231
23	25,000	0	550	200	200	1,500	1,030	7,220	4,830	300	0	2,150	250	0	350	1,000	350	4,900
24	14,900	119	149	60	80	805	775	3,129	2,742	323	89	2,503	209	30	323	656	357	2,503

TABLE 9—Comparison of Absolute Counts per Cubic Millimeter in Sternal Marrow During the Three Trimesters of Pregnancy and for Pregnant and Nonpregnant Women

	Total Nucleated Cell Count per Cu Mm	Granuloblasts (Myeloblasts)	Progranulocytes Type A (Promyelocytes Type A)	Progranulocytes Type S (Promyelocytes Type S)	Eosinophilic Granulocytes (Eosinophilic Myelocytes)	Neutrophilic Myelocytes (Neutrophilic Myelocytes)	Megakaryocytes (Meta myelocytes)	Rhabdocytes (Unsegmented Polymorphonuclears)	Lobocytes (Segmented Polymorphonuclears)	Eosinophils	Basophils	Lymphocytes	Monocytes	Megaloblasts			Disintegrated Cells
														Karyoblasts	Prokaryocytes	Karyocytes	Metakaryocytes
Trimester 1																	
Maximum	65,700	328	900	675	494	4,336	5,913	28,251	8,835	1,140	197	6,300	965	136	1,314	2,628	2,700
Minimum	14,400	0	38	0	28	172	239	2,189	4,050	48	0	2,894	40	0	86	259	28
Average	34,580	63	378	262	218	2,267	2,165	11,659	5,445	371	78	3,975	333	56	749	1,139	944
Trimester 2																	
Maximum	125,000	1,250	2,500	3,500	1,440	13,125	10,270	46,250	11,750	990	125	10,000	612	203	1,875	7,000	2,000
Minimum	15,700	0	69	0	0	659	251	3,077	1,575	18	0	1,686	0	0	251	314	250
Average	41,318	173	462	446	251	3,229	2,623	15,415	5,441	299	47	4,467	245	73	707	1,803	835
Trimester 3																	
Maximum	70,000	635	1,460	1,050	700	7,937	4,900	29,400	8,080	700	191	5,400	732	210	3,937	8,636	2,730
Minimum	16,900	0	0	51	0	391	340	4,901	391	0	0	1,318	0	0	51	51	119
Average	33,937	96	341	362	167	2,138	1,879	11,819	4,613	228	49	3,719	194	61	1,050	1,865	836
Pregnant women																	
Maximum	125,000	1,250	2,500	3,500	1,440	13,125	10,270	46,250	11,750	1,140	197	10,000	965	210	3,937	8,636	2,730
Minimum	14,400	0	0	0	0	172	251	2,189	391	0	0	1,318	0	0	51	51	28
Average	36,764	115	393	366	269	2,552	2,211	10,415	5,111	288	56	4,045	246	64	886	1,662	863
Nonpregnant women																	
Maximum	16,000	279	736	630	514	4,140	4,324	14,490	7,084	642	184	6,520	717	122	1,396	2,904	1,089
Minimum	7,550	0	11	0	0	168	168	1,091	1,132	60	0	1,721	32	0	62	134	43
Average	23,100	89	251	147	147	1,668	1,437	6,048	3,565	246	53	3,428	312	28	616	1,199	453

sedimentation rates of the blood of healthy nonpregnant women (tables 5 and 6) agree well with the values previously established,⁸ and the sedimentation rates of sternal marrow (tables 1 and 5) have apparently not been previously determined. Our results are summarized in table 11. There seems to be a definite tendency for the sedimentation rates to be lower in the marrow than in the blood of the same person. The reason

TABLE 10—*Summary of Average and Range of Values for Sternal Marrow of Pregnant and of Nonpregnant Women from This Study as Compared with the Normal Range for Sternal Marrow as Determined by Young and Osgood*¹

	Normal Range (Male)	Average per Cu Mm	Range (Non pregnant Women)	Average per Cu Mm	Range (Pregnant Women)	Average per Cu Mm
Total nucleated cell count	6,000 to 60,000 per cu mm		7,750 to 46,000 per cu mm	23,100	14,400 to 125,000 per cu mm	36,760
Granuloblasts	0 0 2 0%	0 44%	0 0 - 0 8%	0 3%	0 0 - 1 0%	0 24%
Progranulocytes, type A	0 0 - 5 0	1 48	0 1 2 2	1 0	0 0 2 3	0 93
Progranulocytes, type S	0 0 5 0	1 68	0 0 - 1 4	0 5	0 0 - 2 8	0 82
Eosinophilic granulocytes	0 0 2 0	0 64	0 0 - 1 5	0 5	0 0 2 6	0 40
Neutrophilic granulocytes	0 0 10 0	0 86	1 4 - 11 0	6 0	1 2 - 12 5	6 25
Neutrophilic metagranulocytes	1 0 10 0	7 4	1 4 - 9 4	5 6	1 6 - 9 0	5 46
Rhabdocytes	15 0 35 0	24 1	12 4 34 2	23 7	15 2 47 6	33 3
Lobocytes	7 0 25 0	13 3	10 4 31 0	16 6	1 6 - 37 6	15 7
Eosinophils	0 0 - 2 6	0 8	0 2 - 6 0	1 3	0 0 - 6 0	0 88
Basophils	0 0 - 0 2	0 1	0 0 - 0 8	0 3	0 0 - 1 0	0 2
Lymphocytes	4 0 16 0	10 6	9 2 30 4	16 8	4 5 28 0	12 7
Monocytes	0 0 5 0	2 06	0 0 3 5	1 4	0 0 3 0	0 77
Karyoblasts	0 0 - 0 2		0 0 0 4	0 1	0 0 - 1 0	0 17
Prokaryocytes	0 0 - 5 0	1 5	0 6 4 0	2 5	0 3 - 6 2	2 37
Karyocytes	2 0 15 0	7 0	1 3 - 8 0	5 0	0 3 13 6	4 3
Metakaryocytes	2 0 10 0	5 0	0 4 3 2	1 9	0 2 7 0	2 26
Disintegrated cells	12 8 31 8	20 8	10 5 21 0	16 2	5 5 23 6	12 93

TABLE 11—*Comparison of Sedimentation Rates of Blood and of Sternal Marrow in the Three Trimesters of Pregnancy and for Nonpregnant Women*

	Trimester 1		Trimester 2		Trimester 3		Nonpregnant	
	Blood	Sternal Marrow	Blood	Sternal Marrow	Blood	Sternal Marrow	Blood	Sternal Marrow
Minimum	1/6	0/1	1/6	0/1	2/13	0/2	0/2	0/0
Maximum	8/38	5/25	10/52	8/41	15/65	12/56	6/38	4/35
Average	2/14	2/9	5/29	3/17	7/36	4/24	1/8	1/4

for this is not apparent. Possibly it has to do with the protein-forming function of marrow cells.

SUMMARY

A study of the hematology of the blood and sternal marrow of 40 pregnant and 24 healthy nonpregnant women is summarized in the tables. The ranges of values given in table 10 should prove useful in interpreting the results of studies of the marrow of pregnant and nonpregnant young women.

8 Haskins, H. D., Trotman, F. E., Osgood, E. E., and Mathieu, A. A Rapid Method for Determination of the Sedimentation Rate of the Red Cells with Results in Health and Disease, *J. Lab. & Clin. Med.* **16** 487, 1931. Osgood,² pp 223 and 430.

PHOSPHATASE ACTIVITY IN CHRONIC ARTHRITIS

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The presence of a ferment, phosphatase, in the bones of young rats was demonstrated by Robison¹ in 1932. This ferment hydrolyzes the phosphoric esters of hexosephosphate, glycerophosphate and nucleoprotein. One of the resulting products of such hydrolysis is inorganic phosphorus. Therefore, this ferment plays an important role in the deposition of calcium in bone, in carbohydrate metabolism, in renal metabolism and indirectly in the maintenance of the proper hydrogen ion concentration of blood. Its ubiquitous nature in body tissues has been shown by Bodansky² and Kay³.

So complex are the physiologic functions of phosphatase that the complexity can be matched only by the chemical complexity of the liver itself. All investigators have found an increase of serum phosphatase in such diverse diseases as osteitis deformans,⁴ hyperparathyroidism,⁵ rickets⁵ and obstructive jaundice⁶. The exact significance of

From the Department of Medicine and the Arthritic Clinic of the Rochester General Hospital and the private practice of the authors

1 Robison, R. The Significance of Phosphoric Esters in Metabolism, New York, New York University Press, 1932

2 Bodansky, A. Non-Osseous Origins of Serum Phosphatase. Its Increase After Ingestion of Carbohydrates, *J Biol Chem* **104** 473, 1934

3 Kay, H. D. Phosphatase in Bone Diseases, *J Biol Chem* **89** 249, 1930

4 Woodard, H. Q., Twombly, G. H., and Coley, B. L. A Study of the Serum Phosphatase in Bone Disease, *J Clin Investigation* **15** 193, 1936. Morris, N., and Pedau, O. D. Plasma Phosphatase in Disease. A Review, *Quart J Med* **6** 211, 1937. Bodansky, A. Significance of Phosphatase Variations, *J Biol Chem* **105** 11, 1934. Roberts, W. M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit J Exper Path* **11** 90, 1930

5 Roe, J. H., and Whitmore, E. R. Clinico-Pathologic Application of Serum Phosphatase Determinations, with Special Reference to Lesions of the Bones, *Am J Clin Path* **8** 233, 1938

6 Roberts, W. M. Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit M J* **1** 734, 1933. Cantarow, A. Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, *Internat Clin* **1** 270, 1936

this increase is unknown. Regarding other conditions, notably chronic atrophic arthritis and the healing of bone fractures, dissimilar opinions are held. Kay⁷ and also Bodansky and Jaffe⁸ have found an increase in serum phosphatase during repair of bone fractures, whereas Mitchell,⁹ in a careful study of 75 cases, has found a normal or only slightly elevated value for serum phosphatase. Although no critical analyses of

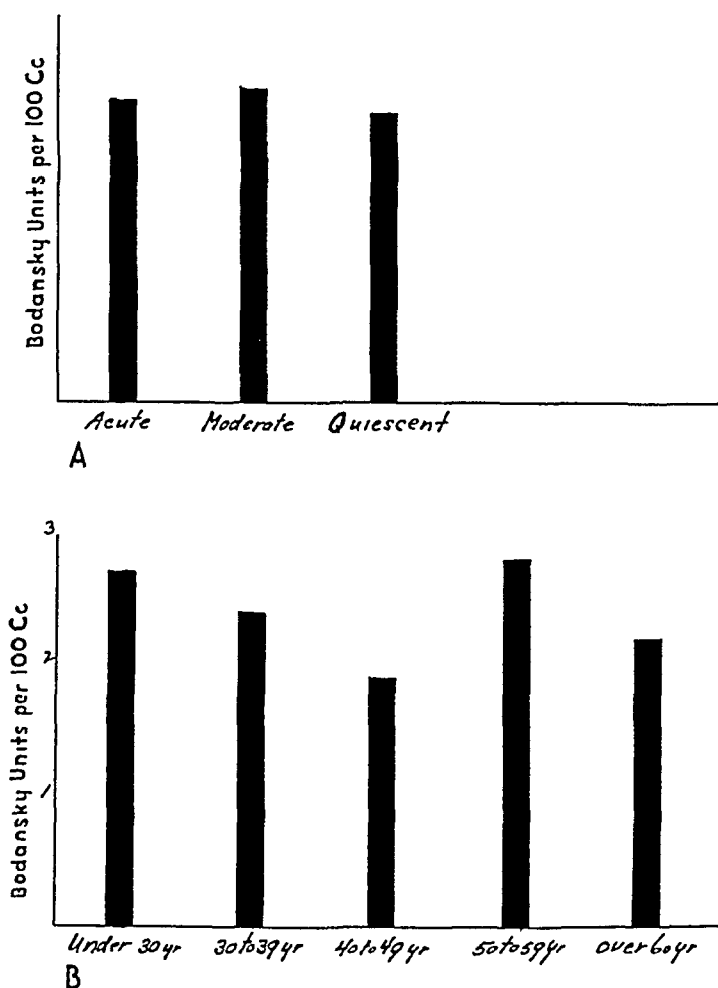


Chart 1—Average phosphatase content of the serum for patients with atrophic arthritis grouped (A) according to their condition at the time of testing and (B) according to age

serum phosphatase in chronic arthritis appear in the literature, Kolmer and Boerner¹⁰ reported a high value for serum phosphatase in cases

7 Kay, H. D. Plasma Phosphatase. The Enzyme in Disease, Particularly in Bone Disease, *J Biol Chem* **89** 249, 1930

8 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. Serum Phosphatase in Diseases of the Bone, Interpretation and Significance, *Arch Int Med* **54** 88 (July) 1934

of chronic arthritis, and Abrams and Bauer¹¹ reported a normal value in cases of atrophic arthritis

The well known pathologic processes of localized osteoporosis associated with chronic atrophic arthritis and the hypertrophic changes of cartilage and bone associated with hypertrophic arthritis suggest the possibility that some abnormal change in serum phosphatase may occur with these conditions. This study is a critical analysis of the values for serum phosphatase for 44 patients with atrophic arthritis and for control groups of patients with hypertrophic arthritis, patients with osteitis deformans and normal healthy persons. The patients with atrophic arthritis were divided into four groups on the basis of the grade of involvement. The group with involvement of grade 1 includes patients having articular pains and stiffness with an increased sedimentation rate

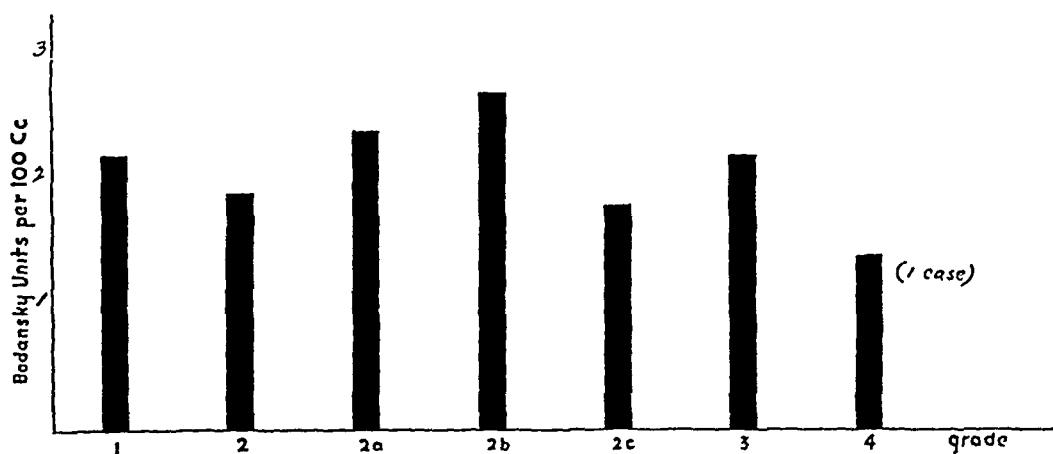


Chart 2—Average phosphatase content of the serum for patients with atrophic arthritis grouped according to the grade of involvement. The figures at the bottom of the chart, denoting the grades of involvement, are to be interpreted as follows: 1, articular pain; 2, swelling of the soft tissues; 2a, 2b, 2c, gradations between 2 and 3; 3, definite articular deformity with early ankylosis; 4, advanced ankylosis (the patient was an arthritic derelict).

and a shift of the Schilling count to the left but no objective signs regarding the joints. The group with involvement of grade 2 includes patients with definite swelling of the soft tissues and localized increase of temperature surrounding the joints involved. The group with involvement of grade 3 includes patients with early fibrous, cartilaginous or bony ankylosis of one or several joints but not patients confined to bed. The group with involvement of grade 4 includes patients confined

9 Mitchell, L. C. Serum Phosphatase in Fracture Repair, *Ann Surg* **104** 304, 1936

10 Kolmer, J. A., and Boerner, F. *Approved Laboratory Technique*, ed 2, New York, D. Appleton-Century Company, 1938, p. 759

11 Abrams, N. R., and Bauer, W. The Treatment of Rheumatoid Arthritis with Large Doses of Vitamin D, *J. A. M. A.* **111** 1632 (Oct 29) 1938

TABLE 1—Data for Patients with Atrophic Arthritis Grouped According to Grade of Involvement

Grade	Case No	Sex of Patient	Age of Patient, yr	Duration of Disease	Condition at Time of Test	Phosphorus Mg	Phosphatase Units
1	27	M	44	7 yr	Moderate	28	19
	32	F	51	12 yr	Moderate	26	25
	Average for group		48	10 yr		27	22
2	3	F	35	8 mo	Moderate	35	25
	42	F	33	25 yr	Moderate	36	10
	11	F	51	2 yr	Quiescent	42	16
	13	F	29	3 yr	Quiescent	26	29
	9	F	27	1½ yr	Quiescent	26	13
	Average for group		35	6 yr		33	19
2a	1	F	34	4 mo	Acute	33	14
	2	M	53	4 mo	Acute	35	23
	8	F	59	1 yr	Acute	38	33
	14	F	59	3 yr	Acute	36	16
	6	F	61	1 yr	Moderate	26	42
	30	M	63	10 yr	Moderate	24	14
	40	F	37	21 yr	Moderate	34	24
	18	F	65	4 yr	Acute	35	32
	19	F	47	5 yr	Quiescent	26	16
	Average for group		53	9 yr		31	24
	10	M	59	1½ yr	Acute	43	53
	33	M	50	12 yr	Acute	24	16
	37	M	45	16 yr	Acute	30	14
2b	39	F	32	19 yr	Acute	34	22
	33	F	38	16 yr	Moderate	34	19
	21	F	38	5 yr	Moderate	25	18
	10a	M	59	1½ yr	Moderate	35	42
	5	F	55	1 yr	Quiescent	26	34
	12	F	53	2 yr	Quiescent	31	17
	12a	F	53	2 yr	Quiescent	35	21
	22	M	39	5 yr	Quiescent	32	34
	23	F	17	6 yr	Quiescent	34	36
	Average for group		45	7 yr		26	27
	31	F	27	11 yr	Acute	34	18
	31a	F	27	11 yr	Moderate	28	18
	Average for group		27	11 yr		31	18
3	4	F	19	8 mo	Acute	32	28
	7	F	38	1 yr	Acute	30	21
	7a	F	38	1 yr	Acute	35	17
	16	M	38	4 yr	Acute	31	34
	20	F	44	5 yr	Acute	37	18
	29	F	44	10 yr	Acute	35	40
	35	F	47	14 yr	Acute	46	10
	15	M	24	3 yr	Moderate	33	20
	17	M	43	4 yr	Moderate	35	29
	24	F	59	6 yr	Moderate	40	29
	25	F	65	7 yr	Moderate	33	30
	44	F	60	30 yr	Moderate	29	17
	36	F	66	15 yr	Acute	32	16
	26	F	38	7 yr	Quiescent	35	26
	34	M	61	12 yr	Quiescent	36	21
	35a	F	47	14 yr	Quiescent	35	10
	43	F	62	30 yr	Quiescent	27	13
	Average for group		47	10 yr		34	
4	28	M	60	10 yr	Acute	30	14

to bed, i e, patients with ankylosis sufficient to prevent them from being ambulatory Gradations of disease between these four grades have been designated with letters of the alphabet The average values for serum phosphatase according to the various grades of involvement were grade 1, 2.2 Bodansky units, grade 2, 1.9 Bodansky units, grade 3a, 2.4 Bodansky units, grade 2b, 2.7 Bodansky units, grade 2c, 1.8 Bodansky units, grade 3, 2.2 Bodansky units, and grade 4 (1 patient), 1.4 Bodansky units Study of these groups of patients fails to indicate conclusively any relation between the degree of articular destruction and the level of serum phosphatase

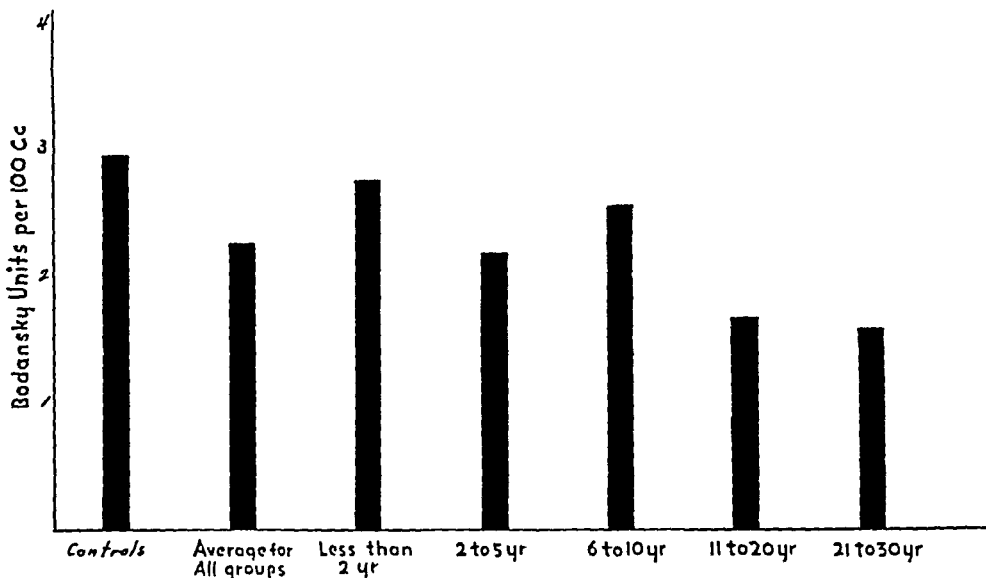


Chart 3—Average phosphatase content of the serum for patients with atrophic arthritis grouped according to the duration of the disease

These patients were also studied according to the duration of the disease The average value for serum phosphatase for the patients with a definite history of atrophic arthritis of less than two years' duration was 2.8 units, two to five years' duration, 2.2 units, of six to ten years' duration, 2.6 units, of eleven to twenty years' duration, 1.7 units, and of twenty-one to thirty years' duration, 1.6 units Therefore, there exists an inverse ratio between the duration of the disease and the level of serum phosphatase Gutman and his associates¹² have shown that the phosphatase content of the serum is slightly increased in generalized osteoporosis in young and middle-aged persons but not in the aged, that is, loss of vitality of bone tissue equals loss in phosphatase activity At first glance one might surmise that the inverse ratio between the duration of the disease and the value for serum phosphatase may be due to the age of the more chronic process rather than to any physio-

12 Gutman, A. B., Swenson, P. C., and Parsons, W. B. Differential Diagnosis of Hyperparathyroidism, *J. A. M. A.* **103**: 87 (July 14) 1934

TABLE 2—Data for Patients with Atrophic Arthritis Grouped According to the Duration of the Disease

Case No	Sex of Patient	Age of Patient Yr	Duration of Disease	Condition at Time of Test	Grade of Involvement	Phos phorus, Mg	Phos phatase Units
Less than 2 years							
1	F	34	4 mo	Acute	2a	33	14
2	M	53	4 mo	Acute	2a	35	23
3*	F	35	8 mo	Moderate	2	35	25
4	F	19	8 mo	Subacute	3	32	28
5	F	55	1 yr	Quiescent	2b	26	34
6	F	61	1 yr	Moderate to acute	2a	26	42
7	F	38	1 yr	Acute	3	30	21
7a	F	38	1 yr	Acute	3	35	17
8†	F	59	1 yr	Acute	2a	38	33
9†	F	27	1½ yr	Quiescent	2	26	13
10§	M	59	1½ yr	Acute	2b	43	53
10a§	M	59	1½ yr	Moderate to acute	2b	35	42
Averages		41				33	28
From 2 to 5 years							
11	F	51	2 yr	Quiescent	2	42	16
12	F	53	2 yr	Quiescent	2b	31	17
12a	F	53	2 yr	Quiescent	2b	35	21
13	F	29	3 yr	Quiescent	2	26	29
14	F	59	3 yr	Acute	2a	36	16
15	M	24	3 yr	Moderate to acute	3	33	20
16	M	38	4 yr	Acute	3	31	34
17	M	43	4 yr	Moderate	3	35	29
18	F	65	4 yr	Subacute	2a	35	32
19	F	47	5 yr	Quiescent	2a	26	16
20	F	44	5 yr	Subacute	3	37	18
21	F	38	5 yr	Moderate	2b	25	18
22	M	39	5 yr	Quiescent	2b	32	34
Averages		46				33	22
From 6 to 10 years							
23	F	17	6 yr	Quiescent	2b	34	36
24	F	59	6 yr	Moderate to acute	3	40	29
25	F	65	7 yr	Moderate to acute	3	33	30
26	F	38	7 yr	Quiescent	3	35	26
27	M	44	7 yr	Moderate	1	28	19
28	M	60	10 yr	Very acute	4	30	14
29	F	44	10 yr	Acute	3	35	40
30	M	63	10 yr	Moderate to quiescent	2a	24	14
Averages		49				32	26
From 11 to 20 years							
31	F	27	11 yr	Acute	2c	34	18
31a	F	27	11 yr	Moderate	2c	28	18
32	F	51	12 yr	Moderate	1	26	25
33	M	50	12 yr	Acute	2b	24	16
34	M	61	12 yr	Quiescent	3	36	21
35	F	47	14 yr	Very acute	3	36	10
35a	F	47	14 yr	Quiescent	3	35	10
36#	F	66	15 yr	Acute	3	32	16
37	M	45	16 yr	Acute	2b	30	14
37a	M	45	16 yr	Quiescent	2b	35	17
38	F	38	16 yr	Moderate	2b	34	19
39	F	32	19 yr	Subacute	2b	34	22
Averages		46				33	17
From 21 to 30 years							
40	F	37	21 yr	Moderate to quiescent	2a	34	24
42	F	33	25 yr	Moderate	2	36	10
43	F	62	30 yr	Quiescent	3	27	13
44	F	60	30 yr	Moderate to acute	3	29	17
Averages		48				32	16
Averages for all groups		47				33	23
Male patients						32	25
Female patients						33	22

* Complicated by mitral stenosis

† Complicated by hyperthyroidism

‡ Complicated by pregnancy

§ Complicated by carcinoma of the prostate with secondary involvement of lung and bone tissue

Complicated by postoperative hypothyroidism

pathologic change associated with chronic atrophic arthritis. However, the average age of the patients who had had chronic arthritis for less than two years was 41, for two to five years, 46, for six to ten

TABLE 3—Data for Patients with Atrophic Arthritis Grouped According to Condition at Time of Test

Case No	Sex of Patient	Age, Yr	Duration	Grade of Involvement	Phosphorus, Mg	Phosphatase Units
Acutely Active Arthritis at Time of Test						
1	F	34	4 mo	2a	33	14
2	M	53	4 mo	2a	35	23
4	F	19	8 mo	3	32	28
7	F	33	1 yr	3	30	21
7a	F	33	1 yr	3	35	17
8	F	59	1 yr	2a	38	33
10	M	59	1½ yr	2b	43	53
14	F	59	3 yr	2a	36	16
16	M	38	4 yr	3	31	34
18	F	65	4 yr	2a	35	32
20	F	44	5 yr	3	37	18
28	M	60	10 yr	4	30	14
29	F	44	10 yr	3	35	40
31	F	27	11 yr	2c	34	18
33	M	50	12 yr	2b	24	16
35	F	47	14 yr	3	46	10
36	F	66	15 yr	3	32	16
37	M	45	16 yr	2b	30	11
39	F	32	19 yr	2b	34	22
Average for group					34	23
Moderately Active Arthritis at Time of Test						
3	F	35	8 mo	2	35	25
6	F	61	1 yr	2a	26	42
10a	M	59	1½ yr	2b	35	42
15	M	24	3 yr	3	33	20
17	M	43	4 yr	3	35	29
21	F	38	5 yr	2b	25	18
24	F	59	6 yr	3	40	29
25	F	65	7 yr	3	33	30
27	M	44	7 yr	1	28	19
30	M	63	10 yr	2a	24	14
31a	F	27	11 yr	2c	28	18
32	F	51	12 yr	1	26	25
38	F	38	16 yr	2b	34	19
40	F	37	21 yr	2a	34	24
42	F	33	25 yr	2	36	10
44	F	60	30 yr	3	29	17
Average for group					31	24
Quiescent Arthritis at Time of Test						
5	F	55	1 yr	2b	26	34
9	F	27	1½ yr	2	26	13
11	F	51	2 yr	2	42	16
12	F	53	2 yr	2b	31	17
12a	F	53	2 yr	2b	35	21
13	F	29	3 yr	2	26	29
19	F	47	5 yr	2a	26	16
22	M	39	5 yr	2b	32	34
23	F	17	6 yr	2b	34	36
26	F	38	7 yr	3	35	26
34	M	61	12 yr	3	36	21
35a	F	47	14 yr	3	35	10
37a	M	45	16 yr	2b	35	17
43	F	62	30 yr	3	27	13
Average for group					32	22

years, 49, for eleven to twenty years, 46, and for twenty-one to forty years, 48. The average age for all these groups was therefore similar, and one must conclude that the duration of the disease affects inversely the value for serum phosphatase.

The degree of articular activity in cases of chronic atrophic arthritis varies considerably. The clinical pattern is one of exacerbations and remissions. We grouped our patients into three divisions, depending on the activity of the arthritis at the time that the study of the serum phosphatase was done, that is, patients with acute arthritis, those with moderately active arthritis and those with quiescent arthritis. The phosphatase content of the serum for the first group was 2.3 units, that for the second group, 2.4 units, and that for the third group, 2.2 units.

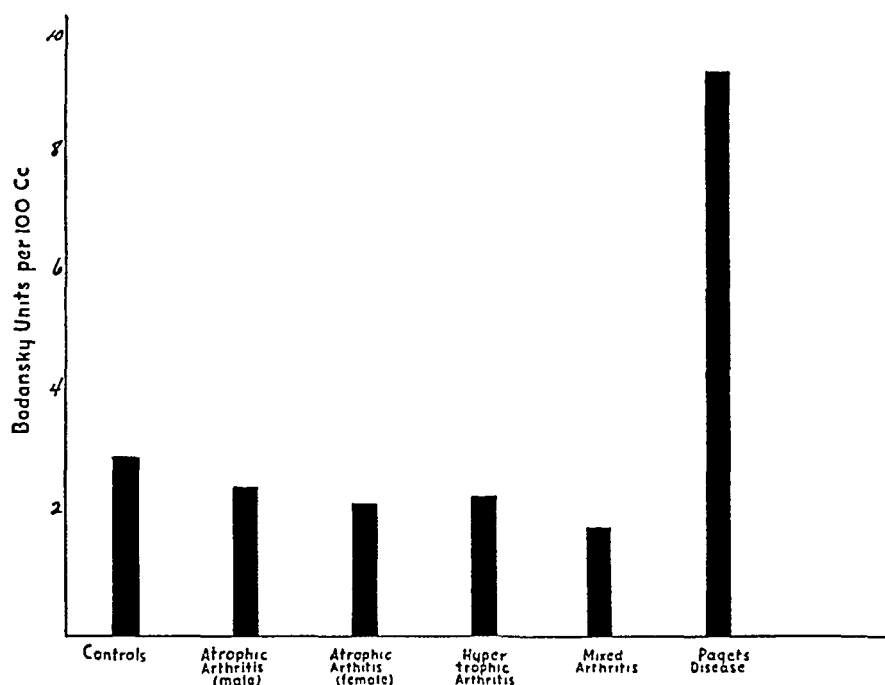


Chart 4—Average phosphatase content of the serum for the different control groups

We must conclude that the activity of the arthritic process does not affect the serum phosphatase.

The control groups consisted of 6 normal persons, 5 patients with osteitis deformans and a small group of patients with hypertrophic arthritis and mixed hypertrophic and atrophic arthritis. The normal persons showed an average value for serum phosphatase of 3 Bodansky units. The average value for serum phosphatase for the 5 patients with osteitis deformans (Paget's disease) was 9.46 units, the variation being 6.24 to 20.20 units. For the small group with hypertrophic arthritis and mixed hypertrophic and atrophic arthritis the values were 2.3 and 1.8 units respectively.

Our findings seem to indicate that a normal level of serum phosphatase is present in cases of chronic atrophic arthritis. The severity of involvement, the stage of the disease and the age of the patient do not affect the level. Long duration of the disease tends to diminish it.

TABLE 4—*Data for Patients with Paget's Disease (Control Study)*

Case No	Age of Patient, Yr	Sex of Patient	Duration of Disease	Extent of Involvement	Phosphorus, Mg	Phosphatase, Units
1	67	F	Unknown	Localized in skull verified by roentgenogram	3.44	8.72
2	67	M	Unknown	Localized in skull verified by roentgenogram ribs and long bones normal	2.96	7.68
2 (repeated)					3.44	7.01
3	73	M	20 yr	Generalized pyramidal head	4.60	14.12
4	81	F	36 yr	Localized, gross change left leg	3.52	6.24
5	69	F	10 to 15 yr	Generalized knee frontal bosses markedly pyramidal verified by roentgenogram	3.80	20.20
Averages					3.55	9.46

TABLE 5—*Phosphorus and Phosphatase Content of the Serum for the Control Groups of Patients*

	Case No	Age, Yr	Sex	Phosphorus, Mg	Phosphatase, Units
Normal persons	1	43	F	3.6	3.0
	2	28	F	3.3	2.3
	3	17	M	3.1	3.7
	4	24	F	2.4	3.6
	5	23	M	3.9	3.1
	6	41	F	2.5	2.5
Average		31		3.1	3.0
Patients with hypertrophic arthritis	45	49	F	3.1	2.6
	46	53	F	4.2	2.4
	47	54	M	3.8	1.7
	48	55	F	2.4	2.1
	49	46	M	2.5	1.6
	50	47	M	2.8	2.1
	51	65	M	3.0	3.0
	52	46	F	3.3	2.5
Average		52		3.1	2.3
Patients with mixed hypertrophic and atrophic arthritis	53	49	F	2.9	1.9
	54	60	F	3.8	1.3
	55	50	F	2.7	1.0
	56	56	F	3.4	1.7
	57	43	F	2.4	3.3
Average		52		3.1	1.8

We found the determination of the level of serum phosphatase valuable in differentiating between articular pains associated with chronic arthritis and the indefinite pains associated with osteitis deformans. It is important to remember that the ages of the patients suffering from hypertrophic arthritis and those of the patients suffering from osteitis deformans were similar. Osteitis deformans is associated in many cases with

hypertrophic arthritis, but in many others the latter condition is not present. One instance of osteitis deformans was accidentally discovered during our study of serum phosphatase. The patient was a white man aged 67, a member of the control group. He had a mild degree of hypertrophic arthritis with associated articular pains, for which he sought relief. After an increased value for serum phosphatase had been noted on two occasions, roentgenograms of the patient's skull, pelvis, ribs and long bones were taken. Findings typical of osteitis deformans were demonstrated on the films.

SUMMARY AND CONCLUSIONS

Determinations of the phosphatase content of the serum were made for 44 patients with atrophic arthritis, 8 patients with hypertrophic arthritis, 5 patients with mixed atrophic and hypertrophic arthritis and 5 patients with osteitis deformans. This same study was made of 6 healthy persons. In the only case of arthritis in which the value for serum phosphatase was above 4.2 units it was later proved that malignant tumor of the prostate gland was present, with secondary involvement of bone and lung tissue. An increase of serum phosphatase in this type of malignant disease has been described by Gutman and his co-workers.¹³ Determination of the phosphatase content of the serum in cases of chronic atrophic and hypertrophic arthritis is, therefore, important in the differential diagnosis. A normal value for serum phosphatase is characteristic of chronic atrophic or hypertrophic arthritis, an abnormal value suggests the possibility of a complicating condition or an erroneous diagnosis of this condition. Determinations of the phosphatase content of the serum should be made a routine procedure in the study of diseases of the bones and joints.

Dr. E. T. Wentworth permitted us to study the patients with Paget's disease who were used as controls in this investigation.

13. Gutman, E. B., Sproul, E. E., and Gutman, A. B. Significance of Increased Phosphatase Activity of Bone at the Site of Osteoplastic Metastases Secondary to Carcinoma of the Prostate Gland, *Am. J. Cancer* **28**: 485, 1936.

ELECTROCARDIOGRAPHIC FINDINGS IN CASES OF VENTRICULAR ANEURYSM

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It is the almost unanimous opinion of those who have studied aneurysm of the ventricle complicating occlusion of the coronary artery that the diagnosis of this condition is a difficult clinical task. The rarity of occurrence of the lesion has been somewhat overemphasized. Libman¹ reported that it was found fifteen times as frequently as Hodgkin's disease, and Applebaum and Nicolson² found aneurysm of the ventricle to have been present in 57 (or 38 per cent) of 150 cases of occlusive disease of the coronary arteries of the atherosclerotic group. Of the 57 aneurysms, 56 were located in the left ventricle.

Pletnew³ has shown the difficulty of diagnosis by purely physical means; he reported 0.5 per cent successful diagnoses in 300 cases. Kahn,⁴ in 1922, stated that roentgenographic and fluoroscopic examination are of little aid in the diagnosis of this condition, but more recently several authors⁵ have detected the sacculation by roentgenographic

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1 Libman, E. Methods of Physical Examination, with Special Reference to Painful Disease of the Thorax and Abdomen, Proc Inter-State Post-Grad M. A., North America (1926), 1927, p. 60.

2 Applebaum, E., and Nicolson, G. Occlusive Diseases of the Coronary Arteries, Am Heart J **10** 662, 1935.

3 Pletnew, D. D. Lasst sich ein Aneurysma der Herzventrikel intra vitam feststellen? Ztschr f klin Med **104** 378, 1926.

4 Kahn, M. H. Aneurysm of the Left Ventricle, Am J M Sc **163** 839, 1922.

5 (a) Fogel, E. I. Aneurysm of the Left Ventricle Following Coronary Infarction in a Living Patient, J A M A **100** 39 (Jan 7) 1933. (b) Steel, D. The Roentgen Diagnosis of Cardiac Aneurysms, *ibid* **102** 432 (Feb 10) 1934. (c) Shookhoff, C., and Douglas, A. H. A Case of Acute Coronary Occlusion with Roentgenographic Evidence of the Early Development of an Aneurysm of the Left Ventricle, Am Heart J **7**.95, 1931. (d) Strandell, B. A Contribution to the Diagnosis of Aneurysm of the Heart, Acta med Scandinav **74** 148, 1930. (e) Ellman, P. Angina with Recent Coronary Thrombosis, Myocardial Infarction and Cardiac Aneurysm, Proc Roy Soc Med **26** 139, 1932. (f) Sigler, L. H., and Schneider, J. J. Diagnosis of Cardiac Aneurysms with Report of Two Cases,

(Footnote continued on next page)

methods Sigler and Schneider^{5f} stated that the electrocardiogram is of no specific diagnostic value in disclosing a cardiac aneurysm. However, these authors did mention the fact that in some instances major deflections directed downward in the second and third leads of the standard electrocardiogram with low voltage upward in lead I may be found.

Because of the grave prognosis of this complication of myocardial infarction and its frequent termination by sudden death with or without

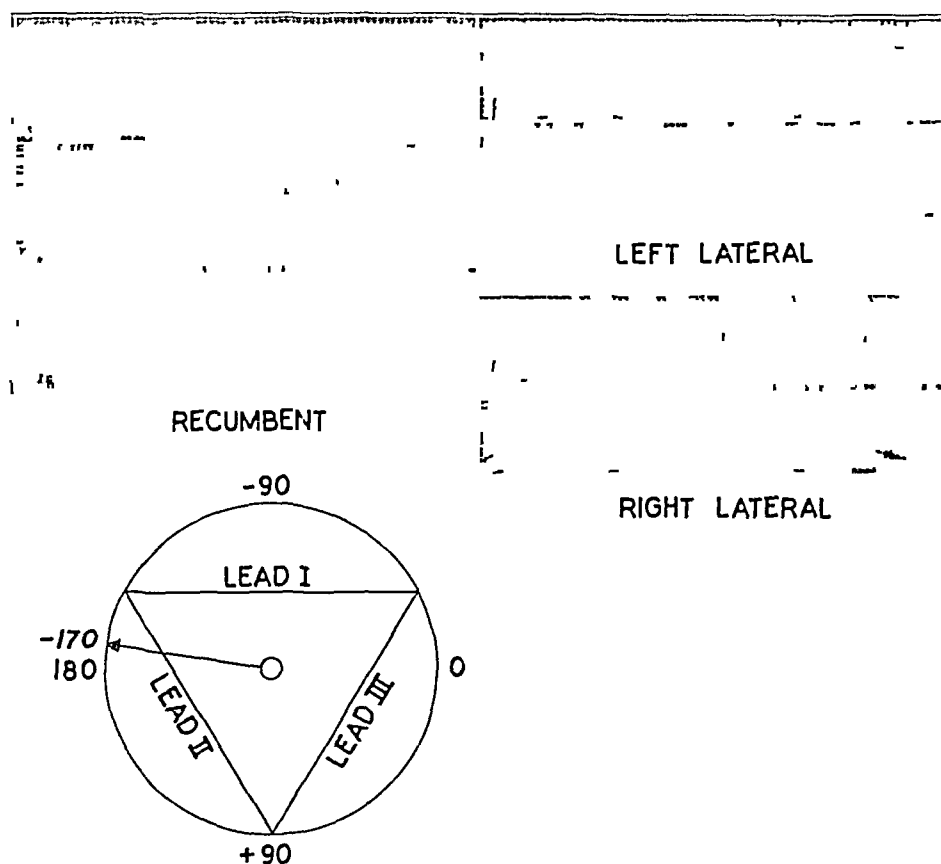


Fig 1 (case 1) —The downward direction of the major deflection with inversion of the T wave and an upright P wave in lead I occurred four weeks after the initial acute occlusion of the coronary artery. The Einthoven triangle illustrates the right axis deviation. The effect of placing the patient in the lateral positions is seen to be negligible. This recording is essentially the same as that taken eight months after the original occlusion of the coronary artery.

rupture, it would seem expedient to utilize all possible diagnostic means to ascertain its presence if such a consequence could thereby be forestalled.

Ann Int Med 8 1033, 1935 (g) Ball, D. Aneurysm of the Heart, Am Heart J 16 203, 1938 (h) Harvier, P., and Caroli, J. Sur un cas d'aneurysme de la pointe du coeur, Paris med 77 30, 1930 (i) East, T. Aneurysm of the Left Ventricle, Proc Roy Soc Med 26 518, 1933

We believe that the electrocardiogram may be of considerable diagnostic value. In several cases we have observed certain cardiographic changes that may be considered a presumptive sign of cardiac aneurysm, and in a slightly greater number of cases we found changes that appeared to be rather suggestive evidence of this lesion.

The contention that study of the electrical activity of the heart may be a valuable aid in the diagnosis of this condition is supported by an analysis of the cases previously reported with accompanying electrocardiograms, together with 5 examples of aneurysm of the ventricle following occlusion of the coronary artery, which we shall present.

The previously published reports show that in 23.5 per cent of the tracings there is a downward direction of the major deflection in lead I. Associated with this finding is inversion of the T wave and an upright P wave in the first lead, the ventricular complex being upright in lead III (fig. 1). By depicting such curves on the Einthoven equilateral triangle, one finds that the electrical axis is in the range of -150 to 180 degrees. In 2 of the 5 cases in our series (40 per cent) this type of record appeared. In 2 other cases of our series (40 per cent), the left axis deviation that has been observed previously in some cases of cardiac aneurysm was found. The left axis deviation is shown on the triangle in figure 4. In this group and in 35.3 per cent of cases reported in the literature, the major deflections were directed downward in leads II and III, with or without low amplitude of the ventricular complex in the first lead (fig. 4).

Cases 1 and 2, which will be described briefly, are examples of those in which right axis deviation occurs (the S_1 type of cardiogram), and case 3 is presented to illustrate those in which left axis deviation is observed (the $S_{2,3}$ type).

REPORT OF CASES

CASE 1—F. F., a 39 year old Russian man, entered the San Francisco Hospital on Nov. 21, 1937, with the complaint of a heavy, nonradiating sensation in the chest of several hours' duration, coming on while at rest. This was associated with marked weakness and nausea. Physical examination showed the patient to be dyspneic, suffering severe pain and clawing at his chest. The temperature was 97°F , the pulse was barely perceptible, and the blood pressure was so low as not to be obtainable. The heart was normal to percussion, but the sounds were faint. The leukocyte count was 14,500 per cubic millimeter, the sedimentation rate was 20 mm in one hour (Linzenmeier method), and the Wassermann reaction of the blood was negative.

The next day the temperature rose to 101 F, and the blood pressure was recorded as 98 mm of mercury systolic and 80 diastolic. The patient complained of moderate precordial pain at that time. An electrocardiogram taken four days after his entry (Nov 25, 1937) is presented in figure 2.

After transient monoplegia of the right arm, he was fairly comfortable until four weeks later, when there was a recurrence of substernal pain with an associated febrile reaction. This was accompanied by changes in the electrocardiogram, namely, downward direction of the ventricular complex in lead II and inversion of the T waves in leads I and II.

Several minor recurrences of pain were noted six weeks after the initial attack. At this time it was found that the apical impulse was palpable in the fifth interspace, 9 cm to the left of the midsternal line. A presystolic gallop rhythm was detected. The blood pressure was 95 mm of mercury systolic and 60 diastolic. There was no evidence of the monoplegia. The electrocardiogram was unchanged.

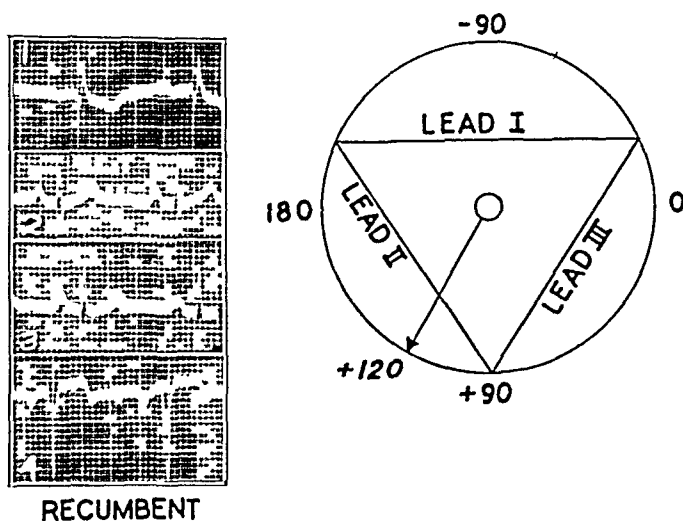


Fig 2 (case 1) —An electrocardiogram taken four days after the initial acute occlusion of the coronary artery, showing the downward direction of the ventricular complex in lead I, with an upright T wave. The right axis deviation is represented on the Einthoven equilateral triangle.

Two months later the patient was admitted to the Mount Zion Hospital with precordial pain which had begun several hours before. Examination showed the apical impulse to be in the sixth interspace 12 cm to the left of the midsternal line and 3 cm inside the left border of cardiac dullness. Gallop rhythm was detected, and the blood pressure was as before, without alternation of the pulse. The electrocardiogram was essentially the same as that shown in figure 1. A roentgenogram of the chest was taken in an attempt to secure further evidence of ventricular aneurysm because of the suggestive cardiographic findings. The roentgenologist, Dr Joseph Levitin, reported at this time that the appearance of the cardiac shadow was consistent with aneurysm of the left ventricle. This film was taken four months after the first coronary occlusion. Eight months after the first attack, the lesion was obvious, as is shown in figure 3. At that time the electrocardiogram was unchanged from that taken four weeks after the original acute thrombosis.

At the time of writing, ten months after the initial occlusion of the coronary artery, the patient is having mild anginal pain only on effort

CASE 2—J M., a 49 year old Irishman, entered the University of California Medical Service of the San Francisco Hospital with a history of dyspnea of six months' duration, which had begun immediately after an attack of precordial pain for which he had been hospitalized for only a few days. Up to the time of entry he had been employed as a laborer. On examination, he was found to be an orthopneic, pyknic man, without edema. There were signs of bilateral pleural effusion, and subcrepitant rales were audible at each pulmonary base. The heart was enlarged to the left, with the apical impulse 9 cm. to the left of the midsternal line in the fifth interspace. The cardiac sounds were normal except for a gallop rhythm, the arterial tension was 96 mm. of mercury systolic and 64 diastolic without pulsus alternans. The liver was palpable and tender. Roentgenographic examination showed signs of bilateral pleural effusion and chronic passive congestion of the lungs, obscuring the cardiac shadow. The Wassermann reaction of the blood

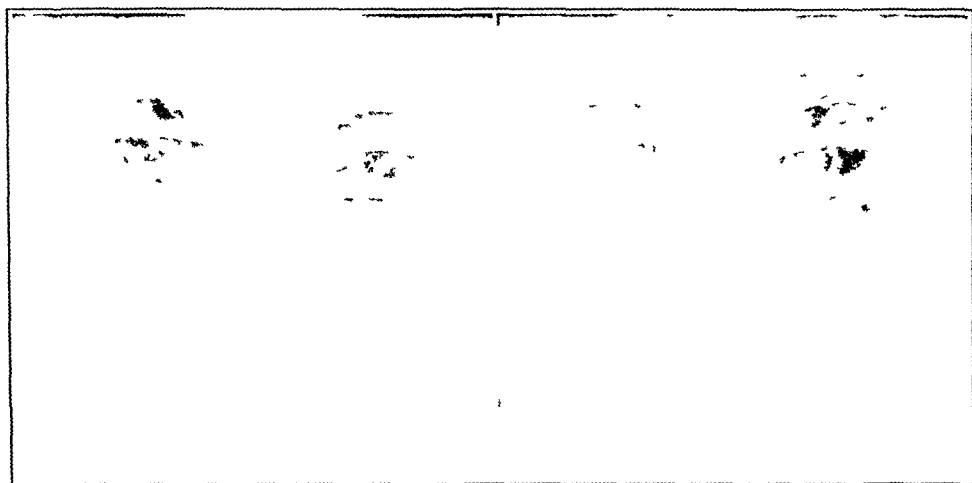


Fig. 3 (case 1)—Roentgenograms taken four and eight months, respectively, after the initial acute occlusion of the coronary artery, showing the increasing size of the aneurysm of the left ventricle

was negative. The electrocardiogram showed a rate of 120, a sinus mechanism, a PR interval of 0.24 second and a normal QRS time, with the chief initial ventricular complex deflected downward in lead I but upright in leads II and III. The T waves were upright in leads II and III but not in lead I. The representation on the Einthoven triangle of deviation of the axis was -160 . Five days after entry the patient died. The anatomic diagnoses were coronary thrombosis, recent and old, of the left anterior branches, mural thrombus in the left ventricle, aneurysmal dilatation of the left ventricle, chronic passive congestion of all organs, ascites, and bilateral hydrothorax.

CASE 3—E S., a 54 year old diabetic woman, had noted dyspnea on exertion for one year, with associated tachypnea when at rest. She failed to recall having had any severe or prolonged precordial pain but had had numerous minor attacks of anginal pain on effort. Physical examination showed an orthopneic woman

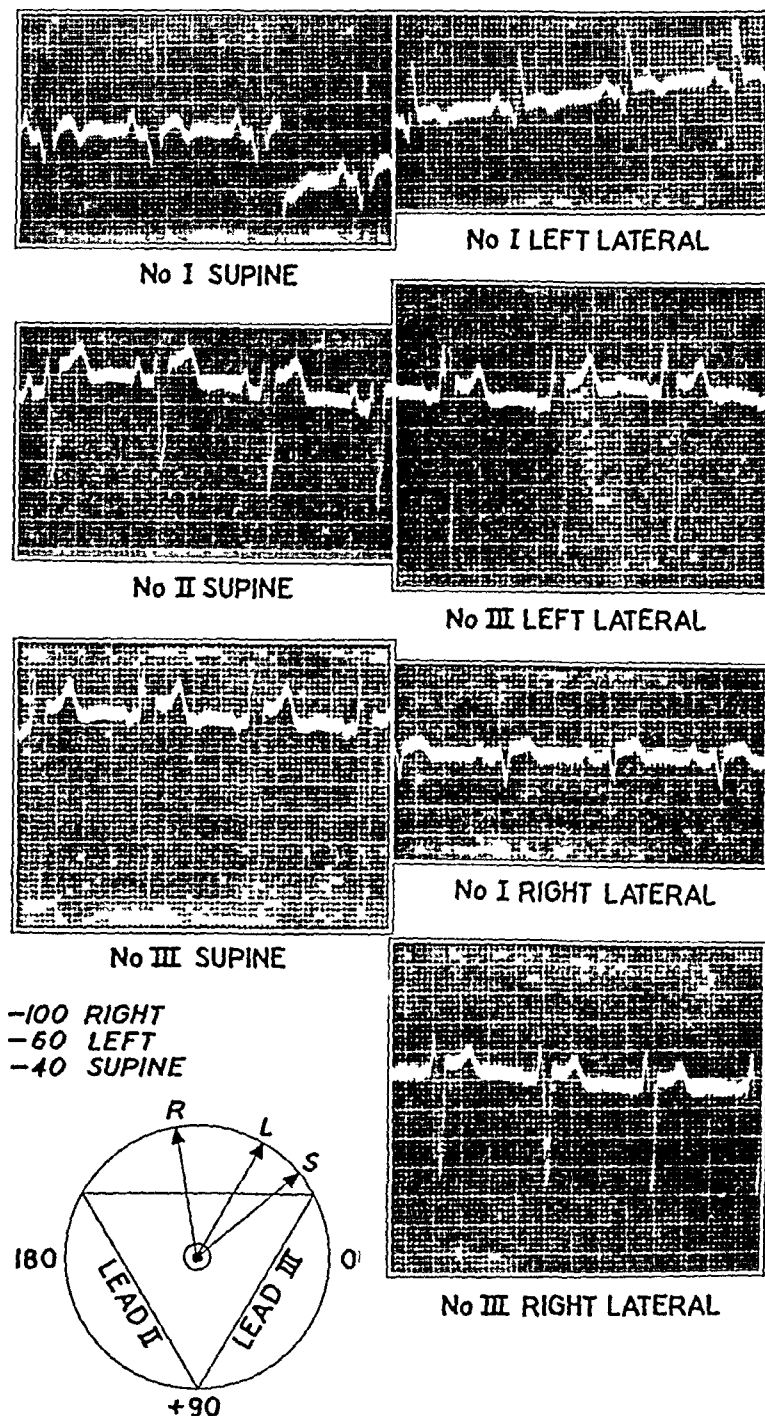


Fig 4 (case 3) —An example of the downward direction of the major deflections in leads II and III, with representation by means of the Einthoven triangle of the axis deviation with the patient in the lateral decubitus positions, as well as supine. This record was made one year after the onset of dyspnea which followed recurrent attacks of precordial pain coming on with effort.

with edema of the ankles and signs of fluid at the bases of both lungs. The heart was greatly enlarged to the left, with the point of maximal impulse in the mid-axillary line in the sixth interspace. There was a definite gallop rhythm but no pericardial friction rub. The blood pressure was 175 mm of mercury systolic and 110 diastolic, with intermittent periods of alternation of the pulse. The results of hemanalysis were not remarkable, and the urinary findings were normal. Transient left hemiplegia was observed twice, on one occasion lasting four hours and on the other two days. One year later, after several attacks of congestive failure, the patient died. The pathologic diagnoses were cardiac hypertrophy with aneurysmal dilatation of the lower portion of the left ventricle, adherent mural thrombus filling the sac, and chronic obliterative pericarditis. Electrocardiograms and a roentgenogram are shown in figures 4 and 5.

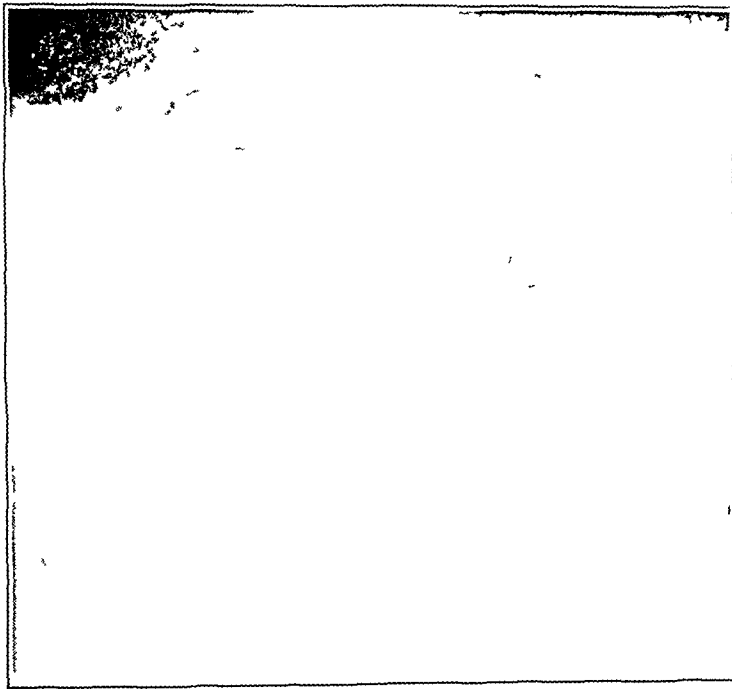


Fig 5 (case 3) —A roentgenogram taken one year after the onset of dyspnea following recurrent attacks of precordial pain coming on with effort, illustrating the aneurysmal dilatation of the left ventricle.

COMMENT

The first 2 of these cases illustrate the electrocardiographic syndrome that was observed to accompany ventricular aneurysm in 27.3 per cent of all cases analyzed. It is of interest to note that recordings made with the patient in the recumbent and in the left and right lateral positions showed no remarkable alteration of the electrical axis of the heart. The electrocardiogram in case 3 is 1 of 2 examples of the S_2 type, which was obtained in 36.4 per cent of all the cases of aneurysm that were studied.

When this downward direction of the major deflections of leads II and III was found, accompanied by an abnormal increase in the QRS

time, notching of the ventricular complexes and T waves that were directed opposite to the major deflections, left bundle branch block was the obvious diagnosis. Conditions of this type were therefore excluded from the group. Their incidence is shown in the accompanying table. It is readily apparent that such tracings can be of no diagnostic value in detecting the presence or absence of cardiac aneurysm. Complete bundle branch block appeared in none of our cases.

In 1 of our cases an electrocardiogram was obtained which, though consistent with occlusion of the coronary artery, did not fall into either of the two diagnostic groups and was not consistent with the diagnosis of bundle branch block.

The table illustrates the frequency of occurrence of the various types of electrocardiographic record. The cases selected from the previously published reports include only those that were considered to be definite instances of ventricular aneurysm and that were illustrated by electro-

Types of Electrocardiogram in Cases of Aneurysm of the Left Ventricle Following Occlusion of the Coronary Artery

	Number of Cases	S ₁	S ₃	Bundle Branch Block	All Others
Previously reported*	17	4 (23.5%)	6 (35.3%)	4 (23.5%)	3 (17.6%)
Present series	5	2 (40.0%)	2 (40.0%)		1 (20.0%)
Total	22	6 (27.3%)	8 (36.4%)	4 (18.2%)	4 (18.2%)

* Kahn⁴, Fogel^{5a}, Shookhoff and Douglas^{5c}, Strandell^{5d}, Ellman^{5e}, Sigler and Schneider^{6f}, Ball^{6g}, Scherf, D., and Erlsbacher, O. Zur Symptomatologie des partiellen Herz aneurysmas, Med. Klin. 30, 1937, 1934; Harvier and Carroll^{5h}, East⁵ⁱ.

cardiograms. In 4 of the 5 cases of our series the condition was proved by pathologic examination to be sacculation resulting from myocardial infarction attendant on occlusion of the coronary artery. The diagnosis in case 1 would seem to be sufficiently well substantiated by the roentgenogram (fig. 3) to permit inclusion in the series.

It cannot be stated with certainty that a downward major deflection with upright P wave and inverted T wave in lead I is an exaggerated Q₁, T₁ type of curve associated only with acute occlusion of the anterior coronary artery. The last tracing in case 1 of our series, obtained ten months after the occlusion, is not dissimilar to that taken four weeks after the initial occurrence of thrombosis, which we believe to have been the event directly leading to the aneurysmal dilatation of the left ventricle. This perpetuation of the right axis deviation also was observed in several cases previously reported.

The electrocardiographic differentiation of ventricular aneurysms producing the S₁ type of electrocardiogram from cor pulmonale and mitral stenosis can be based on the relative rarity of inversion of the T₁ wave in the latter conditions. The various changes in the auricular

complex—such as increase in height, width and notching, which were found by Berliner and Master⁶ in 61 of 69 cases of mitral stenosis—will also be of assistance

Disease of the tricuspid valve, which is so frequently associated with preponderance of the right ventricle, characteristically produces inversion of the T wave in lead III but not in lead I.⁷ Inversion of the T wave in lead I is a rare finding in cases of mitral stenosis except in association with aortic valvulitis. Disease of the aortic valve is certainly one of the more common causes of preponderance of the left ventricle.

Cases of congenital dextrocardia will not be confused with those of ventricular aneurysm when it is observed that the P wave is inverted in the first lead of the electrocardiogram. This finding will also prevent false interpretation from misplacement of the arm electrodes.

Block of the right bundle branch was not found in any of the cases studied, but it should not be confused with conditions suggesting ventricular aneurysm because of the upright T wave in lead I and the usual alterations in the ventricular complex found in cases of bundle branch block.

The $S_{2,3}$ type showing left axis deviation is not necessarily peculiar to cardiac aneurysm. It has been observed in cases of nonsacculated myocardial infarctions as well as in cases of dilated hearts and those presenting marked enlargement of the left ventricle from other causes. It does, however, occur sufficiently often with cardiac aneurysm to warrant consideration of this condition when it is found.

The occurrence of two divergent types of electrocardiogram, one showing left and the other right axis deviation, is hard to explain. It is especially difficult to rationalize, since the anatomic changes are the same in each group. Pathologic examination was made by the usual methods, although detailed examination for incomplete bundle branch block was not performed. In each of the two groups of cases described, as well as in those presenting evidence of lesions of a bundle branch or other equivocal records, apical aneurysms were observed, as were also sacculations of the left ventricle several centimeters superior to the apexes. In over 80 per cent of cases, the aneurysm occurred in that portion of the heart supplied by the anterior descending branch of the left coronary artery. In each of the four groups noted in the table there were instances of such lesions. We have been unable to establish any

6 Berliner, K., and Master, A. M. Mitral Stenosis. A Correlation of Electrocardiographic and Pathologic Observations, *Arch Int Med* **61** 39 (Jan) 1938

7 Master, A. M. Right Ventricular Preponderance of the Heart, *Am J M Sc* **186** 714, 1935

correlation between the location of aneurysm of the left ventricle and the axis deviation produced on the electrocardiogram

The type of electrical axis of the heart in the $S_{2,3}$ group is not surprising and can be explained by any of the causes more generally accepted as producing axis deviation, namely, the position of the center of gravity of the heart, the weight of the myocardial mass, the length of the fibers or the distance that the impulses traverse through the conduction system. It has been observed by Bohning and Katz⁸ that, although preponderance of the left ventricle is most likely to occur with posterior infarction, atypical forms can occur with slow occlusion or with a recent thrombosis superimposed on an older one. It appears from study of the cases in this series that the acuteness of the infarction may be a factor in the causation of the S_1 but not of the $S_{2,3}$ type of electrocardiogram.

By pathologic examination of specimens, it becomes evident that the predominant cardiac mass is the left ventricle. Why this produces an electrical axis deviation usually associated with preponderance of the right ventricle cannot be explained by the older theories of electrical axis deviation. It is paradoxical that the Einthoven equilateral triangle reveals marked right axis deviation with normal ventricular complexes in the presence of enlargement of the left ventricle, yet this fact can apparently be explained by consideration of the relative conducting abilities of the various tissues and fluids involved, as has been shown by Katz and Korey.⁹ These authors demonstrated that blood as an electrical conductor is far inferior to cardiac muscle. It would therefore seem that in contradistinction to the intact wall of the right ventricle, the aneurysmal sac and contained thrombus of the left ventricle may relatively detract from rather than add to the electrical forces.

Not in accord with this explanation is case 3, in which aneurysm of the left ventricle containing a thrombus was present. The wall of the sac was devoid of muscular elements, being composed solely of fibrous tissue. The electrocardiogram in this case revealed marked left axis deviation.

The effects of noncardiac organs which play a role in the distribution of the electrical currents away from the heart itself is not known in such instances as those described. It is probable that variations in the conductivity of the particular tissue in contact with the heart¹⁰ or the

8 Bohning, A., and Katz, L. N. Four Lead Electrocardiogram in Cases of Recent Coronary Occlusions, *Arch Int Med* **61** 241 (Feb.) 1938

9 Katz, L. N., and Korey, H. The Manner in Which the Electrical Currents Generated by the Heart Are Conducted Away, *Am J Physiol* **111** 83, 1935

10 Katz, L. N., Gutman, I., and Ocko, F. H. Alterations in the Electrical Field Produced by Changes in the Contacts of the Heart with the Body, *Am J Physiol* **116** 302, 1936

aneurysm occur. This could possibly explain the differences in the electrocardiograms obtained in the presence of apparently identical lesions. The actual effect of extracardiac transmission of electrical currents cannot be definitely determined at the present time.

Another possible factor causing right axis deviation recordings to be obtained in hearts with left-sided preponderance is the interaction of the rotation of the heart on its anteroposterior axis with that on its longitudinal axis.¹¹ Figure 2 shows the effect on the electrocardiogram of changing the patient from the supine to each lateral position in a case of aneurysm of the left ventricle. It will be observed that the shift of the axis is not of great magnitude. The shift to the right that occurred in case 3 when the patient was placed in the right lateral position, although definite, does not approach that observed in the S_1 type of electrocardiograms taken of patients in the recumbent position. Obviously, simple alteration of the position of the patient will not reveal the respective magnitude of rotation of the heart on its anteroposterior or longitudinal axis. Other methods that have been used experimentally are unfortunately not clinically applicable.

The problem of explaining which cardiac aneurysms will produce the S_1 type and which will show the $S_{2,3}$ type of cardiogram, is not solved as yet. However, the empiric observation that in 63.7 per cent of all cases the electrocardiograms fall into one of two distinct groups, appears to us to be a significant diagnostic point.

SUMMARY

There is an electrocardiographic syndrome, occurring in 27.3 per cent of cases of aneurysm of the left ventricle following occlusion of the coronary artery, which may be considered to be a presumptive sign of this lesion. It consists of a downward directed major deflection in lead I, with inversion of the T wave and an upright P wave. The ventricular complex in lead III is upright.

Another type, occurring in 36.4 per cent of cases, presents ventricular complexes directed downward in leads II and III with an upright major deflection in lead I that may or may not be of low amplitude.

In 18.2 per cent of cases of cardiac aneurysm, the electrocardiogram shows left bundle branch block, and there were a like number of various other equivocal records, which, although consistent with disease of the coronary artery, were not of diagnostic significance.

11 Meek, W. J., and Wilson, A. The Effect of Changes in the Position of the Heart on the QRS Complex of the Electrocardiogram, *Arch. Int. Med.* **36**: 614 (Nov.) 1925. Kountz, W. B., Prinzmetal, M., Pearson, E. F., and Koenig, K. F. The Effect of Position of the Heart on the Electrocardiogram. Electrocardiogram in Revived Perfused Human Hearts in the Normal Position, *Am. Heart J.* **10**: 605, 1935.

Roentgen examination, especially roentgenkymography, would seem to be the most reliable means of corroboration of the diagnosis of ventricular aneurysm and should be performed when one or the other of the two types of cardiogram observed in 63.7 per cent of all cases is obtained.

No correlation between the location of the aneurysm and the specific type of electrocardiogram obtained has been established.

The use of the Einthoven equilateral triangle is a convenient means of visualizing deviation of the axis. However, other more recent theories must be considered in order to explain the two divergent types of cardiogram obtained with pathologically identical lesions.

EFFECTS ON THE CARDIOVASCULAR SYSTEM OF MAN OF FLUIDS ADMINISTERED INTRAVENOUSLY

III STUDIES OF THE GLOMERULAR FILTRATION RATE AS MEASURED BY THE UREA CLEARANCE

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MARK D ALTSCHULE, M D

AND

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Studies of the effects of the administration intravenously of isotonic and slightly hypertonic solutions of crystalloids on the blood volume and on the dynamics of the circulation in normal man have been reported recently from this laboratory¹. After such injections there were noted increased blood volume, with decreased hematocrit reading and plasma protein concentration, increased cardiac output and velocity of blood flow, widening of pulse pressure and transient increase in venous pressure.

In the present investigation the effect of the administration intravenously of isotonic solutions of sodium chloride on renal function in normal man has been studied. The changes which occur in the systemic circulation after this procedure, if shared directly by the glomerular capillary circulation, should affect the glomerular filtration rate, according to the filtration-reabsorption theory of renal function. According to this theory, the glomerular filtration rate is determined by the total functioning glomerular capillary surface, the effective filtration pressure in the glomerular capillaries and the rate of renal blood flow. The increase in blood volume, the lowering of plasma protein concentration and the increase in cardiac output which occur after the intravenous injection of

From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

1 (a) Gilligan, D R., Altschule, M D., and Volk, M C. The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man. I. Studies of the Amount and Duration of Changes in Blood Volume, *J Clin Investigation* **17** 7, 1938. (b) Altschule, M D., and Gilligan, D R. The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man. II. The Dynamics of the Circulation, *ibid* **17** 401, 1938.

fluids would be expected, therefore, so to alter these factors associated with renal function as to increase glomerular filtration, unless specific adjustments in the renal vascular dynamics intervene

MATERIAL AND METHODS

Volumes of 1,000 or 1,500 cc of physiologic solution of sodium chloride were given intravenously at rates of from 28 to 125 cc per minute to 8 adult subjects with normal renal and cardiovascular functions. For convenience, the urea clearance was utilized as a measure of relative glomerular filtration rate. The urea clearance was determined for two periods of approximately one hour each before the injection of fluids, during the injection and for two or three periods embracing the first three hours after injection. The arterial and venous blood pressure, pulse rate, concentration of serum protein and hematocrit value were measured before and immediately after administration of the fluid. The extent of change in blood volume was estimated. The methods utilized in these measurements, with the exception of the urea clearance, were outlined in our earlier studies,¹ the change in blood volume was calculated from the changes in protein concentration and hematocrit value, as described in method A of our previous communication.^{1a} Urea clearance was measured according to the method of Van Slyke, Page, Hiller and Kirk.² Both maximum and standard clearances were calculated in percentages of the mean normal, the values thus being made directly comparable. "Urea plus ammonia" nitrogen was measured by the urease method and by aeration. For calculation of the clearance the volume of urine was corrected for body weight.³ Specimens of urine were obtained from an indwelling catheter in 4 subjects. A light breakfast without tea or coffee was given at 7 a. m., and a light lunch was given to 5 of the patients at 1 p. m. Subjects were requested to drink a glass of water each hour during the control periods so as to insure sufficient output of urine for reliable clearance tests. Specimens of urine were collected from approximately 9 a. m. to 3 p. m.

Because the fluid injected intravenously diluted the plasma, samples of blood for measurement of the urea in the serum were taken before the injection, immediately after the injection and again at the end of either the first or the second period after injection. The urea concentration of the serum taken prior to injection was utilized in the calculation of the urea clearances used as controls. The average of the values before injection and those at the end of injection was used for the calculation of the clearance during the period of injection. Similarly, for the period following injection the average of the values for serum obtained at the beginning and at the end of the period was used in the instances in which the blood urea was measured at the end of this period, in these cases this last value for serum was used for the next two periods. In those instances in which the serum urea was measured at the end of the second period after injection, the values for the first and second periods after injection were calculated by interpolation from the latter

2 Van Slyke, D. D., Page, I. H., Hiller, A., and Kirk, E. Studies of Urea Excretion. IX. Comparison of Urea Clearances Calculated from the Excretion of Urea, of Urea Plus Ammonia, and of Nitrogen Determinable by Hypobromite, *J. Clin. Investigation* **14** 901, 1935.

3 McIntosh, J. F., Moller, E., and Van Slyke, D. D. Studies of Urea Excretion. III. The Influence of Body Size on Urea Output, *J. Clin. Investigation* **6** 467, 1928.

Data on the Effect of the Intravenous Injection of Physiologic Solution of Sodium Chloride on the Urea Clearance and Certain Aspects of the Circulation of Adults with Normal Cardiac and Renal Functions

Case, Sex, Age, Yr	Injection of Solution of NaCl		Period, Min	Serum Urea Nitrogen,* Mg per 100 Cc	Urine Volume, Cc per Min	Urea Clearance, Percentage of Normal	Hemato- crit†	Serum Protein, Gm per 100 Cc	Calcu- lated Increase in Blood Volume, Cc	Venous Pres- sure, Cm H ₂ O
	Amount, Cc	Rate, Cc per Min								
1			0 55		2 49	126				
F			120	11 9	4 55	99				
30	1,000	28	162‡	11 0	1 59	100				
			212	9 9	2 00	101				
			281		1 09	116				
			331		5 00	166				
2			0 60		0 52	100				
M			120	9 0	2 72	101	30 5	6 52		2 6
46	1,000	29	154	7 0	3 32	141	27 8	5 86	320	4 4
			234		4 94	129				
			354	6 8	5 88	113				
3			0 60		0 57	104				
F			152	23 2	0 65	117	38 2	6 86		5 9
44	1,000	32	206	22 0	1 46	107	32 2	5 81	320	10 1
			326	18 4	1 98	112				
			396		1 06	103				
4			0 90		0 41	172				
F			194	11 9	0 52	177		7 26		5 4
42	1,000	33	235	10 5	3 81	161		6 62	250§	8 4
			310		2 64	99				
			369	9 4	0 74	130				
			429		0 75	173				
5			0 58		1 71	108				
M			170	13 9	9 97	115	44 9	6 93		
37	1,000	35	211	13 8	7 00	109	40.8	6 43	60	5 4
			264		4 17	94				5 3
			326	13 6	2 94	101				
			404		1 80	89				
6			0 59		8 05	108				
M			117	6 3	7 33	115	41 5	7 37		7 0
32	1,500	82	162	4 6	4 27	107	34 7	5 45	970	14 7
			220	5 3	6 04	176				
			282		1 81	106				
			342		1 43	135				
7			60		0 43	131				
M			129	8 8	1 46	110	41 8	6 80		5 8
28	1,500	83	166	7 5	1 59	98	34 0	4 97	100	11 8
			223	7 5	0 89	134				
			356		3 11	118				
8			0-63		9 13	78				
M			117	13 2	7 04	73	40 5	8 07		7 6
34	1,500	125	180	11 1	2 86	68	39 5	5 95	700	12 0
			226	10 6	5 66	84				
			351		5 45	74				

* The values given are those obtained at the end of the period for the method used in estimation of mean values for calculating clearance in any given period see section on "Methods"

† In each instance the figures for hematocrit readings serum protein and venous pressure represent values obtained just before and immediately after injection

‡ The period which has been designated with boldface figures in each case is the one during which fluid was injected the value for serum urea in this line is that obtained at the end of injection

§ Plasma volume increase, calculated by assuming the initial hematocrit value to be 40 per cent

value and the one obtained at the end of injection, the value at the end of the second period after injection was used for the calculation of the clearance in the last period

RESULTS

The concentration of serum protein and the hematocrit value decreased after the injection of fluids in all of the 7 cases in which these measurements were made. The decreases in protein concentration were approximately 25 per cent in the 3 instances in which 1,500 cc of fluid was given at rates of from 82 to 125 cc per minute (table). The calculated blood volume showed increases varying from 60 to 970 cc, the larger increases occurring in cases in which the larger volumes of fluid were injected at the faster rates (table). The pulse rate and the arterial blood pressure were not significantly altered. The venous pressure increased during injection in 6 of 7 studies, the average increase being 4 cm of water and the greatest increase 8 cm (case 6, table). These results accord with our earlier observations¹

The values for urea clearance obtained during the period of injection of fluids and during the one hour period after the end of injection showed no consistent changes from those obtained during control periods. In 1 instance (case 2) the clearance during the period of injection was 40 per cent higher than that in the control periods, during the first period after the injection the clearance was 40 per cent lower than the average control value in 1 instance (case 4) and 60 per cent higher in another instance (case 6). Similarly, there were no consistent changes in clearance during the later periods of study, in 1 of the 8 studies, the clearance value for a later period was considerably higher (case 1) than the average control value.

COMMENT

Peters⁴ reviewed the evidences that the area of the glomerular filtering surface, the renal blood flow, the osmotic pressure of the plasma proteins and the glomerular capillary pressure are important factors in determining the glomerular filtration rate, according to the filtration-reabsorption theory of renal function. Since the intravenous injection of fluids as carried out in the present studies induces increased blood volume, increased cardiac output and lowering of the concentration of the plasma proteins (table),¹ this procedure should increase glomerular filtration, unless specific changes in the renal circulatory system intervene.

Our studies demonstrate no effect on the urea clearance of the combination of changes in systemic circulation occurring after the injection of isotonic solutions of sodium chloride intravenously. The occasional high or low results obtained in a single one hour period during or after

⁴ Peters, J. P. *Body Water. The Exchange of Fluids in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

the end of injection in a few of the experiments (table) are interpreted as not significant with respect to the injection of fluid, similar results have been obtained by others who have studied the normal variations in urea clearance during several successive one hour periods. It is to be noted that the increases in blood volume and decreases in plasma protein concentration were pronounced in the subjects receiving 1,500 cc of fluid at rapid rates (cases 6, 7 and 8, table), it was found in our earlier studies^{1a} that after such injections changes in the blood volume and plasma protein were still appreciable up to approximately two hours after the end of injection. Peripheral vasodilatation, as evidenced by flushing of the skin, occurred in a majority of the subjects in the present study. Presumably, increases in cardiac output and velocity of blood flow occurred during the period of injection and during at least a part of the subsequent period of measurement of urea clearance.^{1b}

We have utilized the urea clearance test as a relative measure of glomerular filtration rate. Urea is reabsorbed by the tubules so that the amount of blood cleared of urea per minute does not represent an absolute measure of glomerular filtration rate. However, since the maximum urea clearance varies proportionately with the clearances of creatinine, sucrose, inulin and xylose,⁵ the test is generally accepted as a relative measure of glomerular filtration rate. Values for the urea clearance as expressed in percentages of the average normal are presented in the table so that standard and maximum clearances are directly comparable.

The absence of increases in glomerular filtration rate with the changes in systemic circulation occurring after the administration of fluids intravenously seems to result from specific adjustments in the renal vascular dynamics, afforded by the peculiar anatomic and vasomotor characteristics of the renal vascular system.

There are numerous other examples in the literature which demonstrate constancy of glomerular filtration rate in spite of changes in systemic circulation. Thus, although the cardiac output and the arterial blood pressure are increased by strenuous muscular exercise, the urea clearance is not increased, and even may be decreased, under such conditions.⁶ The glomerular rate is not affected by the injection of

5 Winkler, A. W., and Parra, J. The Measurement of Glomerular Filtration. Creatinine, Sucrose, and Urea Clearances in Subjects Without Renal Disease, *J. Clin. Investigation* **16** 859, 1937. Shannon, J. A., and Smith, H. W. The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, *ibid* **14** 393, 1935. Van Slyke and others.²

6 MacKay, E. M. Studies of Urea Excretion. V. The Diurnal Variation of Urea Excretion in Normal Individuals and Patients with Bright's Disease, *J. Clin. Investigation* **6** 505, 1928. Van Slyke, D. D., Alving, A., and Rose, W. C. Studies of Urea Excretion. VII. The Effects of Posture and Exercise on Urea Excretion, *ibid* **11** 1053, 1932.

epinephrine⁷ The glomerular filtration rate is not increased in patients with high blood pressure due to essential hypertension,⁸ nor does it decrease when the arterial blood pressure decreases either spontaneously or after unilateral renal denervation⁹ Either no change or a slight decrease in glomerular filtration rate has been observed when peripheral vasodilatation and decrease in arterial blood pressure are brought about by the administration of sodium nitrite to normal subjects and patients with primary hypertension¹⁰ The glomerular filtration rate is not increased in artificially induced hyperpyrexia, with its accompanying increased cardiac output¹¹ Normal glomerular filtration obtains in patients with hypoproteinemia due to protein malnutrition or to the nephrotic state⁴

Decreased glomerular filtration is found, on the other hand, in the presence of shock,⁴ when the blood pressure is lowered during spinal anesthesia,¹² and in oliguria due to dehydration¹³ Effective treatment of such conditions with intravenous injections of fluids undoubtedly results in increased glomerular filtration rate It appears that the renal circulation in man can so adjust itself as to maintain relative constancy of glomerular filtration, except under conditions of extreme demand on the systemic circulatory system

Keutmann and Bassett¹⁴ reported an increase in urea clearance in a nephritic patient on the day after a transfusion of 800 cc of plasma, they suggested that the increased glomerular filtration rate resulted from increased plasma volume In an unreported study, we noted no change in urea clearance after the transfusion of 500 cc of blood in a nephritic patient with a urea clearance of 5 per cent of normal, in the case of another nephritic patient, with a control clearance of 4 per

7 Chasis, H , Ranges, H A , Goldring, W , and Smith, H W The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, *J Clin Investigation* **17** 683, 1938

8 Roelsen, E Determination of the Permeability of Tissues to Creatinine by the Holten and Rehberg Method in Hypertension, *Hospitaltid* **75** 579, 1932

9 Page, I H The Effect on Renal Efficiency of Lowering Arterial Blood Pressure in Cases of Essential Hypertension and Nephritis, *J Clin Investigation* **13** 909, 1934

10 Weiss, S, and Ellis, L B Influence of Sodium Nitrite on the Cardiovascular System and on Renal Activity in Health, in Arterial Hypertension and in Renal Disease, *Arch Int Med* **52** 105 (July) 1933

11 Farr, L E, and Moen, J K Effect of Induced Hyperpyrexia on the Urea Clearance of Rheumatic Patients, *Am J M Sc* **197** 53, 1939 Chasis and others⁷

12 Lassen, H C A, and Husfeldt, E Kidney Function and Blood Pressure, *J Clin Investigation* **13** 263, 1934

13 Chesley, L C Renal Excretion at Low Urine Volumes and the Mechanism of Oliguria, *J Clin Investigation* **17** 591, 1938

14 Keutmann, E H, and Bassett, S H Studies on the Mechanism of Proteinuria, *J Clin Investigation* **16** 767, 1937

cent of normal, 1,000 cc of physiologic solution of sodium chloride administered intravenously at the rate of 28 cc per minute did not affect the urea clearance

Medes and Herrick¹⁵ observed a parallelism between renal blood flow, as measured by the thermostromuhr, and creatinine clearance in the dog. Van Slyke and his associates,¹⁶ using the method of explanting the kidney, also demonstrated that in the dog spontaneous variations in urea clearance parallel chiefly variations in renal blood flow. Chasis and his co-workers⁷ measured clearances of diodrast, phenolsulfonphthalein and inulin simultaneously in man to obtain information on the effect on the glomerular filtration rate of changes in renal blood flow brought about by certain drugs. If it is correct to assume that the diodrast clearance is an exact¹⁷ or proportional measurement of renal blood flow, the results of these authors indicate that the glomerular filtration rate in man may not be affected by changes in renal blood flow.⁷ These authors pointed out that this may obtain, since effective glomerular capillary pressure and effective glomerular filtering surface are affected by the state of both the afferent and the efferent arterioles of the kidney.

Schmitz¹⁸ studied the glomerular filtration rate, as measured by the creatinine clearance, after the intravenous injection of physiologic solution of sodium chloride in dogs. In contrast to our results in man, he found large increases in clearances in the dog. The findings of Chasis and his co-workers⁷ indicate that in man the glomerular filtration rate does not vary directly, within certain limits, with renal blood flow, whereas other investigators have found that in the dog the filtration rate does vary with renal blood flow. Van Slyke and his associates¹⁶ pointed out that the variations in urea clearance produced by alterations in diet and other changes are much greater in the dog than in man. The difference between the results of Schmitz after the

15 Medes, G., and Herrick, J. F. Blood Flow to the Kidney and Creatinine Clearance, *Proc Soc Exper Biol & Med* **31** 116, 1933

16 Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S. Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption and Diuresis. The Mechanism of Urea Excretion, *Am J Physiol* **109** 336, 1934

17 The average effective renal blood flow of 775 cc per square meter of body surface per minute obtained by these authors for normal man at rest appears too great, being approximately 35 per cent of the total output of the left ventricle with the subject at rest. Calculations from the data of E. K. Marshall Jr. (Studies on the Cardiac Output of the Dog. I. The Cardiac Output of the Normal Unanesthetized Dog, *Am J Physiol* **77** 459, 1926) on the cardiac output of the unanesthetized non-pregnant dog and of Van Slyke and his associates¹⁶ on the renal blood flow in the dog measured by the method of Fick indicate that for this species the renal blood flow is only 16 per cent of the output of the left ventricle.

18 Schmitz, H. L. Studies on the Action of Diuretics. I. The Effect of Euphyllin and Salyrgan upon Glomerular Filtration and Tubular Reabsorption. *J Clin Investigation* **11** 1075, 1932

intravenous administration of fluids in dogs and our results in man may be attributable to differences based on species

Since no exact regimen of administration of fluids by mouth was invoked in these studies,¹⁹ the nature of the diuresis brought about by the injections of physiologic solution of sodium chloride cannot be described exactly. It is evident, however, that diuresis was not prompt (table). Similarly, the same volume of isotonic solution of sodium chloride when administered orally to normal man is eliminated gradually over a period of several hours, in contrast to prompt elimination of similar volumes of distilled water.⁴

SUMMARY

The effect of the intravenous administration of 1,000 to 1,500 cc of physiologic solution of sodium chloride on the glomerular filtration rate, as measured relatively by the urea clearance, of adults with normal renal and cardiovascular functions has been studied. The fluids were injected at rates sufficiently rapid to cause increases in blood volume and cardiac output, decreases in plasma protein concentration, transitory increases in venous pressure and evidences of peripheral vasodilatation.

The glomerular filtration rate was not changed by the injections of fluid, even in those cases in which great changes in the systemic circulation were shown.

The absence of increase in glomerular filtration in the presence of hypervolemia, increased cardiac output and lowered protein osmotic pressure, as induced in our studies, appears to result from specific adjustments in the renal vascular dynamics. No information is available from our studies as to the nature of such renal adjustments.

These results, together with those obtained by other investigators in certain clinical conditions and after the administration of certain drugs demonstrate that the rate of glomerular filtration may not be affected in the presence of large changes in the systemic circulation.

19 Subjects were requested to drink a glass of water each hour during the control periods, so as to insure sufficient output of urine for reliable clearance tests; the overgenerous cooperation of patients 5, 6 and 8 explains the water diuresis observed in the control periods in these studies.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XI DIETS CONTAINING DRIED EXTRACTED LIVER

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The effect of feeding diets containing varying percentages of dried whole liver to intact, unilaterally nephrectomized and partially nephrectomized rats has been presented¹ In order to study the effect of removing the water-soluble extracts, dried extracted liver was fed to a similar group of animals This investigation is concerned with the effect of diets containing increasing amounts of dried extracted liver on the weight of the kidney and of the heart, the blood pressure, the renal function and the relation of the concentration of urea in the blood and that in the urine of intact, unilaterally nephrectomized and partially nephrectomized rats

EXPERIMENTAL METHODS

White rats, raised in the Laboratory of Physiological Chemistry of the University of Virginia, were maintained on a stock diet until they were between 60 and 70 days old, when unilateral nephrectomy or subtotal nephrectomy was performed The details of the operative procedure and the care of the animals have been described elsewhere¹

Renal function was determined by a modified Addis urea clearance test² and was represented by the urea ratio, $\frac{\text{urea excretion per hour}}{\text{urea in 100 cc of blood}}$ Blood pressure was read by direct cannulation of the carotid artery while the animal was under ether anesthesia The heart and kidney were weighed immediately after the animal was killed The surface area was calculated from the weight of the animal by the formula of Lee³ The weight of the heart and of the kidney per unit of surface

From the Laboratory of Physiological Chemistry, the University of Virginia

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1 Chanutin, A Experimental Renal Insufficiency Produced by Partial Nephrectomy III Diets Containing Whole Dried Liver Liver Residue and Liver Extract, Arch Int Med **54** 720 (Nov) 1934

2 Chanutin, A, and Ludwig, S Experimental Insufficiency Produced by Partial Nephrectomy V Diets Containing Whole Dried Meat, Arch Int Med **58** 60 (July) 1936

3 Lee, M O Am J Physiol **89** 24, 1929

area is expressed by $\frac{H}{S} \frac{W}{A}$ and $\frac{K}{S} \frac{W}{A}$, respectively. The dried extracted liver was the residue from cold storage hog liver which had been thoroughly extracted with hot water (approximately 90 C). The animals were fed the experimental diets from seventy to one hundred and seventy-five days. The diets (table 1) are designated EL 10, EL 20, EL 40, EL 60 and EL 80 in accordance with the percentage of dried extracted liver used.

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls (Intact and Unilaterally Nephrectomized Rats)—The effects of diets on 161 intact and 96 unilaterally nephrectomized rats are shown in table 2, in which are recorded observations of the duration of the experiment, the surface area, the blood pressure, the $\frac{\text{heart weight}}{\text{surface area}}$ ratio, the $\frac{\text{kidney weight}}{\text{surface area}}$ ratio, the total solids of the kidneys, the urea ratio and the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio.

TABLE 1—Composition of Rations

Diet	Concentration of Component in Diet, Percentage						
	Dried Extracted Liver	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Nitrogen
EL 10	10	62	14	5	5	4	15
EL 20	20	52	14	5	5	4	29
EL 40	40	32	14	5	5	4	51
EL 60	60	12	14	5	5	4	72
EL 80	80	6		4	6	4	96

Blood Pressure and Heart Weight It is interesting that only 7 of the 161 intact rats and 3 of the 96 unilaterally nephrectomized rats had blood pressures over 140 mm of mercury and none above 150 mm. In these few animals the elevation in blood pressure did not appear to be related to the concentration of extracted dried liver in the diet. The $\frac{H}{S} \frac{W}{A}$ ratios, as presented in table 2, are fairly constant for all diets, with one exception. The average value of the $\frac{H}{S} \frac{W}{A}$ ratio is appreciably lower for the unilaterally nephrectomized rats on the EL 80 diet.

Kidneys The $\frac{K}{S} \frac{W}{A}$ ratios for the intact and the unilaterally nephrectomized rats, except those for the unilaterally nephrectomized rats receiving the EL 80 diet, increase progressively with the increase in the intake of extracted liver. When the $\frac{K}{S} \frac{W}{A}$ ratios for the intact and the unilaterally nephrectomized animals receiving the EL 10 diet are expressed as unity, the respective ratios for the animals on the diets from EL 10 to EL 80 are as follows: for the intact animals,

TABLE 2—Observations on Control Animals Fed a Variety of Diets

Renal Condition and Diet	Value	Duration of Experiment, Days	Surface Area	Blood Pressure, Mm	Heart Weight		Kidney Weight		Total Solids of the Kidneys, Percentage	Urea Ratio	Urea Ratio
					Surface Area × 100, Gm	Weight, Gm	Surface Area × 100, Gm	Weight, Gm			
2 kidneys EL 10	Minimum	72	222	106	0.140		0.334		22.3	31	25
	Maximum	161	386	146	0.176		0.490		24.8	66	43
	Average	128 ± 5.8	298 ± 6.3	128	0.162		0.390 ± 0.007		23.4	41 ± 1.9	39 ± 1.4
1 kidney EL 10	Rats	32	32	32	32		32		5	24	24
	Minimum	114	200	116	0.130		0.267		23.4	22	30
	Maximum	121	334	142	0.181		0.361		26.2	40	41
2 kidneys EL 20	Average	116 ± 1.9	290 ± 7.1	130	0.163		0.297 ± 0.008		24.9	31 ± 1.8	36 ± 1.2
	Rats	13	13	128 ± 1.3*	0.163 ± 0.001*				13	11	11
2 kidneys EL 20	Minimum	78	280	112	0.139		0.348		23.2	37	26
	Maximum	168	428	148	0.183		0.475		25.8	72	50
	Average	132 ± 7.6	342 ± 7.6	126	0.163		0.413 ± 0.009		24.6	55 ± 2.4	38 ± 1.2
1 kidney EL 20	Rats	25	25	25	25		25		6	20	20
	Minimum	59	280	114	0.138		0.276		21.5	32	31
	Maximum	177	466	148	0.181		0.370		26.7	62	33
2 kidneys EL 40	Average	135 ± 8.6	356 ± 7.3	128	0.161		0.289 ± 0.007		24.4	46 ± 1.6	43 ± 1.5
	Rats	26	26	127 ± 1.2*	0.163 ± 0.002*				18	22	22
2 kidneys EL 40	Minimum	83	276	112	0.148		0.375		23.0	35	25
	Maximum	174	428	140	0.187		0.435		25.4	100	47
	Average	131 ± 6.5	340 ± 8.0	123	0.167		0.470 ± 0.009		24.1	60 ± 3.5	38 ± 1.5
1 kidney EL 40	Rats	25	25	25	25		25		7	21	21
	Minimum	102	278	106	0.148		0.293		22.0	31	33
	Maximum	188	463	126	0.170		0.417		26.6	62	43
2 kidneys EL 60	Average	149 ± 12.7	350 ± 12.5	121	0.159		0.376 ± 0.015		25.1	70 ± 1.0	38 ± 1.1
	Rats	11	11	122 ± 1.3*	0.163 ± 0.002*				8	9	9
2 kidneys EL 60	Minimum	80	286	108	0.141		0.421		21.7	41	40
	Maximum	174	426	144	0.199		0.455		24.7	101	49
	Average	148 ± 6.0	342 ± 6.8	123	0.166		0.380 ± 0.011		22.9	68 ± 2.7	38 ± 1.0
1 kidney EL 60	Rats	37	37	37	37		37		11	20	20
	Minimum	110	278	112	0.126		0.354		22.9	32	24
	Maximum	126	392	144	0.184		0.502		26.1	66	45
2 kidneys EL 80	Average	114 ± 1.4	338 ± 6.8	126	0.161		0.411 ± 0.010		25.0	48 ± 1.8	36 ± 1.6
	Rats	23	23	124 ± 1.2*	0.163 ± 0.002*				21	21	14
2 kidneys EL 80	Minimum	85	252	110	0.131		0.470		22.3	44	24
	Maximum	166	398	146	0.194		0.635		25.2	92	44
	Average	129 ± 4.8	324 ± 6.4	123	0.157		0.385 ± 0.009		24.4	78 ± 2.5	33 ± 0.8
1 kidney EL 80	Rats	13	13	42	42		42		10	17	11
	Minimum	97	268	110	0.114		0.424		22.9	34	20
	Maximum	120	376	148	0.178		0.511		24.8	75	52
2 kidneys EL 80	Average	108 ± 2.2	312 ± 7.8	120	0.147		0.386 ± 0.008		23.9	64 ± 2.4	39 ± 1.5
	Rats	22	22	123 ± 1.1*	0.153 ± 0.002*				11	21	21

* Average and standard error for control animals on a specific diet

1, 106, 115, 133 and 137, for the unilaterally nephrectomized animals, 1, 10, 126, 138 and 130. A similar comparison of the total solids of the kidneys gives practically the same result.

TABLE 3—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 10 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of the Kidneys, Percentage	Urea Ratio
				Surface Area, × 100	Surface Area × 100		
1	97	252	130	0.158	0.215		12
2	97	274	134	0.196	0.287		18
3	97	231	186	0.254	0.175		4
4	97	244	158	0.215	0.240		8
5	97	341	132	0.174	0.186		19
6	97	265	144	0.181	0.176		
7	97	248	136	0.180	0.165		8
8	97	340	128	0.181	0.188		
9	97	240	130	0.161	0.175		13
10	97	262	132	0.171	0.166		8
11	97	280	128	0.173	0.174		
12	122	256	142	0.177	0.162	25.8	13
13	124	275	136	0.188	0.232	22.7	19
14	124	230	230	0.253	0.228	17.5	
15	124	238	116	0.168	0.182	23.2	7
16	125	297	162	0.173	0.261		11
17	125	265	146	0.167	0.149		6
18	125	283	198	0.197	0.376		8
19	125	258	158	0.171	0.284		11
20	125	230	168	0.166	0.174		13
21	125	265	152	0.179	0.196		12
22	125	274	166	0.182	0.302		
23	125	348	154	0.190	0.219		
24	125	266	136	0.160	0.200		
25	125	389	124	0.197	0.246	24.0	22
26	125	308	144	0.202	0.187	22.0	10
27	125	289	156	0.197	0.244	21.7	9
28	125	242	228	0.250	0.232		5
29	125	258	126	0.178			14
30	127	334	126	0.200	0.192		13
31	127	383	134	0.192	0.266		10
32	127	248	130	0.168	0.170		15
33	127	205	176	0.164	0.168		7
34	127	314	132	0.172	0.197		22
35	127	232	138	0.165	0.160		9
36	127	220	132	0.151	0.174		5
37	127	328	250	0.235	0.281		7
38	127	295	198	0.197	0.422		
39	127	302	134	0.179	0.233		
40	127	324	128	0.188	0.222		10
41	140	265	160	0.195	0.219		6
42	152	333	182	0.201	0.323		10
43	152	250	118	0.161	0.225		
44	152	301	152	0.222	0.231		8
45	152	274	134	0.174	0.274		19

Urea Ratios The average urea ratios for the animals with intact kidneys receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80 diet are 44, 55, 60, 68 and 58, respectively. There is a significant progressive increase in the values, followed by a marked decrease for the animals receiving the EL 80 diet. The average values

for the unilaterally nephrectomized animals are 31, 46, 50, 48 and 46, respectively. The ratio for the animals receiving the EL 10 diet is the only low value obtained, while the remaining ratios are fairly constant regardless of diet.

TABLE 4—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight	Kidney Weight	Total Solids of the Kidneys, Percentage	Urea Ratio
				Surface Area, $\times 100$	Surface Area, $\times 100$		
1	124	355	122	0.161	0.265	20.3	7
2	124	285	164	0.167	0.376	17.7	16
3	124	354	138	0.166	0.238	22.0	9
4	124	307	126	0.176	0.304	19.2	18
5	124	340	168	0.189	0.248	20.4	16
6	126	379	130	0.178	0.323	17.1	12
7	126	374	208	0.243	0.367	14.3	7
8	126	285	198	0.280	0.264	16.1	3
9	126	408	166	0.189	0.313	18.6	17
10	126	380	142	0.197	0.371	18.9	15
11	131	354	128	0.181	0.244		12
12	131	328	176	0.197	0.268		21
13	132	370	158	0.179	0.297		12
14	132	374	182	0.189	0.266		16
15	132	398	144	0.213	0.290		8
16	133	362	120	0.164	0.238		25
17	133	320	162	0.191	0.262		19
18	133	302	132	0.173	0.314		16
19	133	302	170	0.187	0.256		14
20	133	302	224	0.253	0.212		14
21	133	379	160	0.220	0.202		8
22	133	427	154	0.183	0.272		29
23	133	270	166	0.190	0.270		
24	133	341	194	0.206			
25	133	372	202	0.232	0.350		
26	133	346	136	0.171	0.218		29
27	146	306	162	0.233	0.462		
28	146	366	132	0.181	0.266		18
29	150	380	186	0.259	0.362		7
30	150	310	154	0.195	0.242		3
31	150	289	170	0.248	0.390		9
32	150	314	182	0.293	0.206		5
33	150	322	146	0.242	0.480		22
34	150	374	166	0.196	0.334		4
35	154	291	146	0.191	0.358		
36	154	278	194	0.228	0.232		8
37	154	345	148	0.177	0.294		7
38	154	380	146	0.182	0.374		11
39	154	289	164	0.193	0.474		7
40	154	350	158	0.180	0.306		17
41	154	360	148	0.193	0.264		

The $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios are 39, 38, 38, 38 and 33 for the intact rats receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80 diet, respectively, for the unilaterally nephrectomized rats the ratios are 36, 43, 38, 36 and 39, respectively. Despite the wide variations in diet, it is seen, these ratios are extremely constant for both the intact and the unilaterally nephrectomized rats.

TABLE 5—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of the Kidneys, Percentage	Urea Ratio
				Surface Area, × 100	Surface Area, × 100		
1	71	346	126	0 174	0 280		19
2	71	256		0 148	0 250		13
3	71	265	162	0 164	0 445		10
4	71	350	132	0 159	0 390		20
5	71	280	122	0 151	0 243		28
6	71	307	132	0 160	0 273		25
7	73	380	148	0 179	0 558		10
8	73	291	136	0 200	0 250		9
9	73	268	134	0 148	0 286		12
10	73	283	136	0 155	0 383		12
11	73	292	134	0 137	0 258		16
12	101	244	124	0 162	0 465	15 0	10
13	101	341	130	0 171	0 362	13 4	5
14	101	303	142	0 170	0 514	12 6	6
15	103	360	126	0 177	0 293	20 8	17
16	103	308	124	0 166	0 264	20 7	22
17	103	291	178	0 228	0 264	15 1	6
18	103	308	128	0 160	0 231	20 8	
19	103	374	142	0 179	0 294	21 8	
20	125	372	164	0 191	0 440	16 3	13
21	125	411	156	0 180	0 322	18 0	20
22	125	334	176	0 223	0 633	10 6	3
23	125	356	130	0 174	0 356	16 7	12
24	125	373	126	0 165	0 318	22 0	28
25	126	291	134	0 155	0 514	14 0	13
26	126	356	144	0 186	0 487	13 2	8
27	126	285	136	0 173	0 348	18 6	13
28	126	320	184	0 232	0 384	13 4	3
29	126	303	132	0 156	0 247	21 6	27
30	126	299	186	0 216	0 594	14 7	10
31	127	379	144	0 199	0 140	16 7	9
32	127	320	150	0 163	0 447	15 7	10
33	127	364	134	0 165	0 410	17 0	15
34	127	386	138	0 210	0 488	14 9	7
35	127	358	172	0 227	0 573	17 6	4
36	127	346	134	0 187	0 416	19 7	
37	127	374	142	0 195	0 523	14 8	10
38	127	356	192	0 236	0 578	11 7	
39	132	266	198	0 195	0 450	16 7	
40	132	283	146	0 172	0 309	18 9	8
41	132	270	162	0 179	0 341	16 9	10
42	132	275	136	0 159	0 290	19 9	
43	132	285	144	0 159	0 358	16 8	8
44	132	278	136	0 152	0 245	20 8	12
45	132	263	166	0 197	0 261	15 9	
46	132	299	158	0 159	0 346	15 0	
47	132	258	214	0 222	0 385	14 0	4
48	132	280	128	0 167	0 350	20 0	9
49	132	302	158	0 184	0 315	18 7	11
50	132	280	162	0 205	0 495	14 0	6
51	134	276	126	0 162	0 305	18 0	6
52	134	343	154	0 250	0 635	12 8	5
53	134	379	140	0 182	0 374	20 8	15
54	134	291	156	0 147	0 452	13 6	
55	134	263	136	0 153	0 340	13 6	13
56	142	283	133	0 169	0 421		
57	142	275	202	0 207	0 583		4
58	142	285	210	0 209	0 312		4
59	142	283	196	0 199	0 500		8

From table 2 it appears that blood pressures below 140 mm of mercury and urea ratios above 30 may be accepted as normal for all animals

TABLE 6—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 60 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of the Kidneys, Percentage	Urea Ratio
				Surface Area, $\times 100$	Surface Area $\times 100$		
1	89	314	160	0.220	0.550	14.7	8
2	89	265	190	0.177	0.510	13.5	11
3	89	270	154	0.179	0.508	12.9	5
4	89	306	162	0.183	0.473	12.9	6
5	89	334	140	0.193	0.431	17.4	16
6	89	307	154	0.183	0.455	13.2	
7	91	256	142	0.181	0.629		
8	91	297	136	0.179	0.513		15
9	91	304	158	0.191	0.545		6
10	96	324	158	0.232	0.726		6
11	98	374	142	0.168	0.622		22
12	93	274	142	0.166	0.476		12
13	98	248	136	0.202	0.484		
14	98	291	123	0.158	0.481		17
15	98	266	134	0.146	0.395		17
16	104	256	196	0.228	0.302	13.5	3
17	104	256	162	0.223	0.362	12.6	3
18	104	289	158	0.205	0.458	17.8	9
19	104	262	134	0.175	0.295	18.8	13
20	106	334	142	0.220	0.650	13.0	9
21	106	289	152	0.180	0.331	18.6	15
22	106	301	198	0.195	0.450	14.6	9
23	107	336	190	0.199	0.113		9
24	107	307	170	0.180	0.604		29
25	107	283	122	0.151	0.372		23
26	109	313	152	0.176	0.642	12.8	
27	109	244	200	0.205	0.620	11.7	5
28	109	283	148	0.186	0.534	15.7	14
29	109	260	166	0.196	0.633	15.0	15
30	109	266	198	0.186	0.546	13.8	10
31	113	297	148	0.185	0.442	16.8	11
32	113	278	176	0.180	0.538	13.6	7
33	113	316	172	0.174	0.471	17.4	7
34	113	286	168	0.210	0.376	13.8	19
35	126	260	144	0.186	0.770	12.7	10
36	126	274	138	0.164	0.491	16.5	
37	126	285	136	0.168	0.740	14.0	18
38	146	270	146	0.141	0.388		10
39	146	295	136	0.155	0.417		17
40	146	310	146	0.183	0.730		7
41	146	270	124	0.151	0.390		15
42	146	295	128	0.157	0.308		22
43	148	270	144	0.135	0.454		12
44	148	244	122	0.151	0.293		10
45	148	308	156	0.164	0.854		10
46	148	246	130	0.200	0.686		3

Partially Nephrectomized Rats—The duration of the experiment, the surface area, the blood pressure, the $\frac{H}{S} \frac{W}{A}$ ratio, the $\frac{K}{S} \frac{W}{A}$ ratio, the total solids of the kidney and the urea ratio for partially nephrectomized rats receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80 diets are shown in detail in tables 3 to 7

Charts 1 to 5 were prepared from these tables to facilitate comparison of the effects of the different diets on the blood pressure, $\frac{K}{S} \frac{W}{A}$ ratio, the urea ratio and the relation between the concentration of urea in the blood and in the urine

Blood Pressure The data on blood pressure are summarized in chart 1. The group receiving the EL 20 diet had the greatest percentage

TABLE 7—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 80 per Cent Dried Extracted Liver*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of the Kidneys, Percentage	Urea Ratio
				Surface Area, $\times 100$	Surface Area, $\times 100$		
1	82	232	152	0.172	0.361		12
2	86	280	140	0.153	0.438		17
3	89	254	144	0.158	0.478		18
4	89	248	146	0.165	0.529		
5	96	248	118	0.154	0.433		17
6	96	246	132	0.163	0.661		15
7	96	292	156	0.167	0.838		14
8	100	289	142	0.155	0.475	21.1	18
9	101	274	152	0.177	0.685	12.3	10
10	101	278	206	0.192	0.781	11.6	12
11	101	323	164	0.177	0.623	11.6	14
12	101	348	152	0.172	0.593	17.9	21
13	106	234	156	0.160	0.410		13
14	106	272	152	0.187	0.534	14.8	8
15	106	270	174	0.202	0.740	12.9	16
16	106	242		0.195	0.526	14.9	11
17	107	316	136	0.170	0.415		24
18	107	320		0.171	0.447		24
19	107	297	138	0.161	0.446		10
20	107	258	148	0.153	0.330		18
21	109	274	136	0.148	0.318	19.7	20
22	117	260	180	0.161	0.353		15
23	117	258	124	0.162	0.696		20
24	122	304	180	0.170	0.456	17.7	17
25	122	313	134	0.174	0.577	17.0	20
26	122	222	126	0.150	0.408	17.1	11
27	122	304	144	0.169	0.511	18.0	24
28	138	289	194	0.145	0.655	13.9	11
29	138	278	134	0.162	0.717	13.9	7
30	138	275	172	0.146	0.510	19.6	22
31	138	254	134	0.150	0.476	16.2	13
32	138	286	156	0.175	0.606	13.4	8
33	138	232	122	0.178	0.480	13.2	4

of animals with pressures above 160 and above 180 mm of mercury, and the group receiving the EL 80 diet had the smallest percentage of hypertensive animals. In order to determine the effect of diet on the incidence of unusually high pressures, the percentage of rats with blood pressures above 200 mm in the group receiving each diet was listed as follows: EL 10, 16; EL 20, 22; EL 40, 14; EL 60, 13; and EL 80, 3. The highest individual blood pressure, 250 mm, was noted in an animal receiving the EL 10 diet.

A positive relation between the height of blood pressure and the degree of cardiac hypertrophy has been demonstrated⁴ by calculating the coefficient of correlation between the blood pressure and the $\frac{H}{S} \frac{W}{A}$ ratio. In the present study the coefficients with their probable errors, listed according to the diet, are as follows: EL 10, 0.76 ± 0.04 , EL 20, 0.49 ± 0.08 , EL 40, 0.59 ± 0.06 , EL 60, 0.44 ± 0.08 , and EL 80, 0.49 ± 0.09 . A fairly high degree of correlation was obtained for the animals receiving the EL 10 diet, and a substantial relation was noted for the remaining groups.

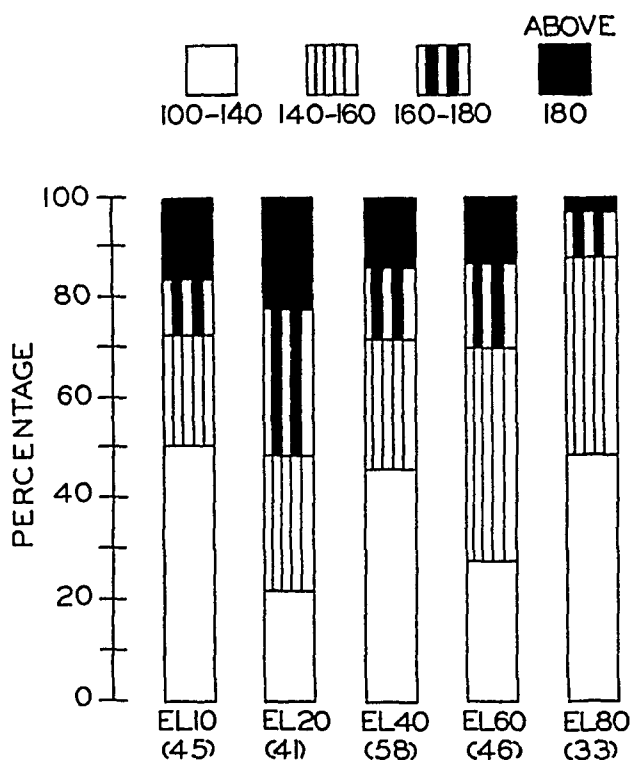


Chart 1—Effect of diet on the blood pressure of partially nephrectomized rats. The figures in parentheses represent the number of animals.

Kidneys The data on the total solids of the kidneys per hundred square centimeters of surface area are presented in chart 2. This value is more reliable than the $\frac{K}{S} \frac{W}{A}$ ratio, since variations in the water content of the stump of the kidney are eliminated. The average values for the dried kidneys expressed in milligrams with standard errors are 47 ± 2.1 , 56 ± 2.3 , 64 ± 1.8 , 74 ± 3.1 and 85 ± 3.4 , for the animals receiving the EL 10, the EL 20, the EL 40, the EL 60 and the EL 80

⁴ Chanutin, A., and Barksdale, E. E. Experimental Renal Insufficiency Produced by Partial Nephrectomy. II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, *Arch Int Med* **52**: 739 (Nov.) 1933.

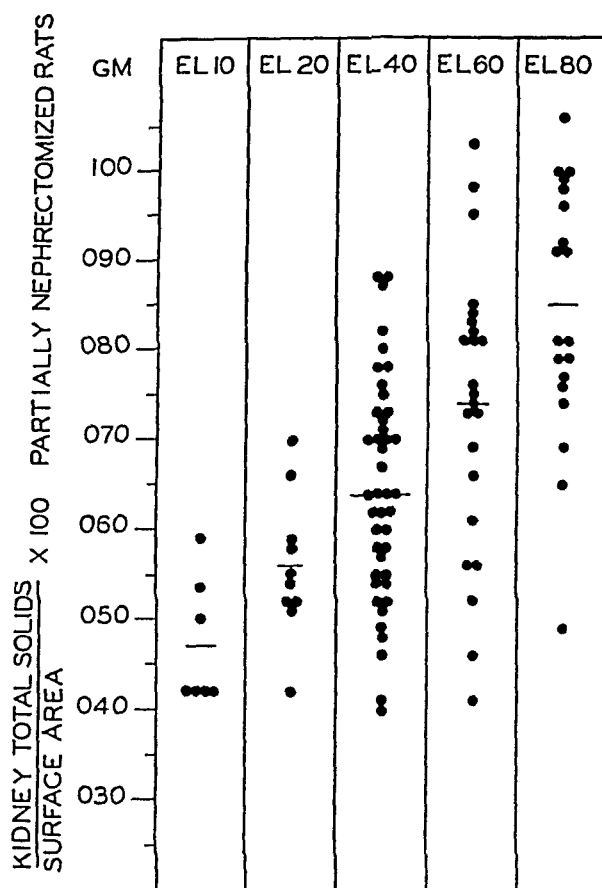


Chart 2—Effect of diet on the total solids of the kidneys per hundred square centimeters of surface area

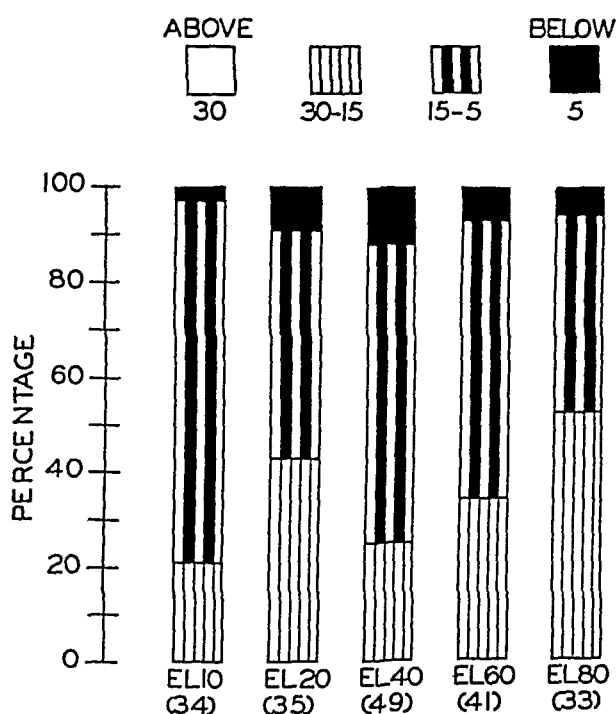


Chart 3—Effect of diet on the urea ratio of partially nephrectomized rats
The figures in parentheses represent the number of animals

diet, respectively. When the average value for the animals receiving the EL 10 diet is expressed as 1, the respective ratios for the diets are 1.0, 1.19, 1.36, 1.57 and 1.81. This is interpreted to mean that

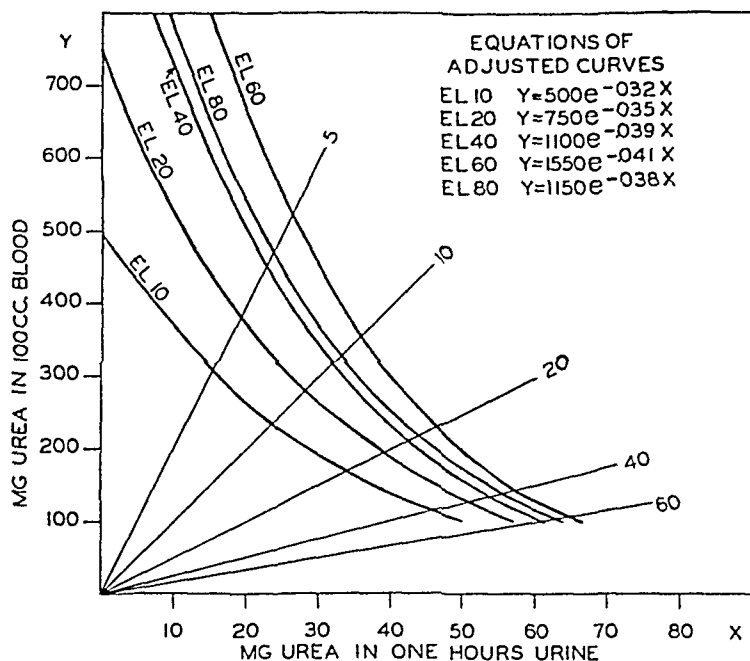


Chart 4—Relation of the adjusted curves for blood urea and urine urea

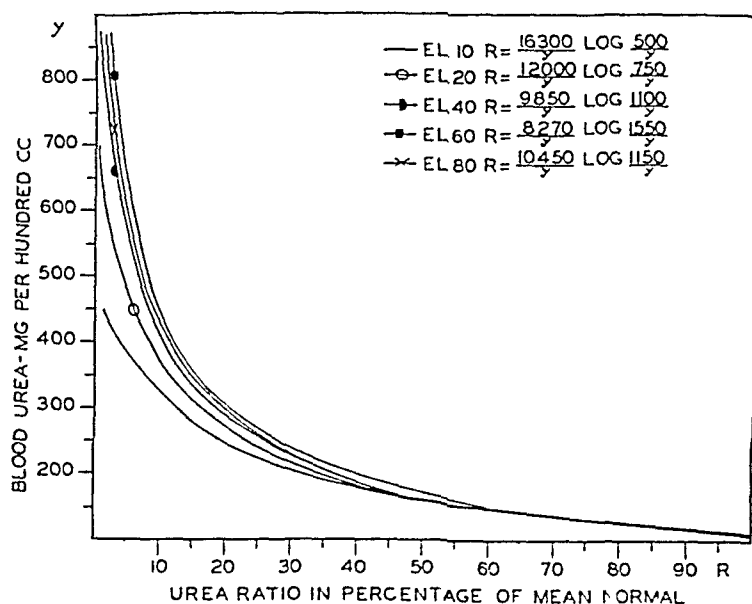


Chart 5—Relation between the concentration of urea in the blood and the urea ratio expressed as percentage of the mean normal value

hypertrophy of renal tissue progresses with the increase in the ingestion of protein

Urea Ratios The incidence of the urea ratios is summarized in chart 3. The group receiving the EL 40 diet had the highest

percentage of ratios below 5. All groups with the exception of that receiving the EL 80 diet had a large percentage of relatively low ratios, indicating marked renal insufficiency.

Effect of Diet on the Blood Urea and Urine Urea. Urea clearance was determined from the ratio $\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc of blood}}$. At any given urea ratio wide variations in the concentrations of urea in the urine and the blood were obtained for each diet, and these data are presented in chart 4. It is seen that the values for blood urea are progressively increased with increase in the intake of protein at any given urea ratio, except for the animals receiving the EL 80 diet. The inability of animals with severe renal insufficiency to excrete administered urea was accompanied by extraordinarily marked retention of urea in the blood, particularly with the higher concentrations of protein in the diet.

The curves in chart 5 represent an analysis of the effect of diet on the concentration of urea in the blood at any given urea ratio expressed as percentage of the mean normal. The concentration of urea in the blood is not affected appreciably by diet until renal insufficiency is encountered.

SUMMARY

The effect of feeding diets containing various percentages (10, 20, 40, 60 and 80) of dried extracted liver to rats with intact kidneys and to unilaterally nephrectomized and partially nephrectomized rats has been studied.

The ingestion of these diets by intact and by unilaterally nephrectomized animals was accompanied by the following changes:

1. Blood pressure was not affected by diet.
2. The $\frac{\text{heart weight}}{\text{surface area}}$ ratio was fairly constant for all groups except that a low value was observed for the unilaterally nephrectomized rats fed the EL 80 diet.
3. The $\frac{\text{kidney weight}}{\text{surface area}}$ ratio increased progressively with increase in the intake of protein except that the unilaterally nephrectomized rats receiving the EL 80 diet had a low ratio.
4. The urea ratio per gram of kidney was fairly constant for all diets, indicating a direct relation between the degree of renal hypertrophy and the degree of renal function.

The syndrome in partially nephrectomized rats was affected by the percentage of extracted liver in the following manner:

1. The frequency and degree of hypertension were not directly related to the amount of extracted liver in the diet. The most marked hypertension was noted in the animals receiving the EL 20 diet, and

the lowest incidence occurred in the group receiving the EL 80 diet. A close relation between the height of blood pressure and the degree of cardiac hypertrophy was demonstrated for all dietary groups.

2 The total solids of the kidneys increased progressively with increase in ingestion of protein.

3 The animals receiving the EL 40 diet appeared to have the greatest degree of renal insufficiency, as determined by the urea ratio.

4 The concentration of urea in the blood and in the urine at any given ratio increased with increase in the intake of protein except in the group receiving the EL 80 diet.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XII DIETS CONTAINING DRIED EXTRACTED MEAT

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The effect of diets containing varying concentrations of dried whole beef muscle on the intact, the unilaterally nephrectomized and the partially nephrectomized rat has been dealt with in a previous paper¹ The present report is concerned with the effect of feeding diets containing dried extracted beef muscle on the blood pressure, heart weight, kidney weight and renal function of intact, unilaterally nephrectomized and partially nephrectomized rats

EXPERIMENTAL METHODS

The experimental procedures have been described in previous papers¹ Briefly, they are as follows Partial nephrectomy involved the removal of 80 to 90 per cent of total kidney tissue by a two stage operation, blood pressure readings were obtained by cannulation of the carotid artery, urine was collected for the concentration test for twenty-four hours from the rats deprived of food and water, and a modified urea clearance test of Addis¹ was used for determining renal function

The five experimental diets used were designated EM 10, EM 20, EM 40, EM 60 and EM 80 in accordance with the percentage of dried extracted meat (table 1), prepared by repeated extraction of cold storage lean beef muscle by hot water (approximately 90 C) The extracted meat residue was subjected to hydraulic pressure to get rid of the last trace of extract and then dried in steam heated containers The experimental animals were subjected to the respective dietary regimens for a minimum of seventy-five days and a maximum of one hundred and seventy-five days

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls (Intact and Unilaterally Nephrectomized Rats)—The blood pressure, $\frac{\text{heart weight}}{\text{surface area}}$ and $\frac{\text{kidney weight}}{\text{surface area}}$ ratios, concentration of urine, urea clearance and plasma nonprotein nitrogen concentrations

From the Laboratory of Physiological Chemistry, the University of Virginia

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1 Chanutin, A, and Ludwig, S Experimental Renal Insufficiency Produced by Partial Nephrectomy V Diets Containing Whole Dried Meat, Arch Int Med 58 60 (July) 1936

for 238 intact and unilaterally nephrectomized rats on the respective diets are summarized in table 2. All of these data could not be obtained for every animal. All rats were in good health when killed.

Blood Pressure and Heart Weight. Of the 147 individual blood pressures for the intact rats, only 4 were above 140 mm. Eleven of the 90 unilaterally nephrectomized animals had blood pressures between 140 and 150 mm. The mean values for blood pressures of the intact and the unilaterally nephrectomized rats on each diet differed so little that the figures for both groups were used in calculating the standard error for the respective diets. It is noted that there is little difference in the mean blood pressures for the various groups. The average $\frac{H}{S} \frac{W}{A}$ ratios are fairly constant for all diets. This reflects the constancy of the average blood pressures and the relation between the $\frac{H}{S} \frac{W}{A}$ ratio and the blood pressure.

TABLE 1—*Composition of Rations*

Diet	Concentration of Component in Diet, Percentage						
	Extracted Meat	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Nitrogen
EM 10	10	62	14	5	5	4	1.91
EM 20	20	52	14	5	5	4	3.07
EM 40	40	32	14	5	5	4	5.54
EM 60	60	12	14	5	5	4	8.39
EM 80	80	6		4	6	4	11.10

The $\frac{K}{S} \frac{W}{A}$ ratios increase progressively with an increase in the intake of protein. If the average $\frac{K}{S} \frac{W}{A}$ ratio for the intact animals on the EM 10 diet is considered as 1, the intact animals on the EM 20, the EM 40, the EM 60 and the EM 80 diet show comparative ratios of 1.06, 1.18, 1.26 and 1.50, respectively, if the ratio for the unilaterally nephrectomized animals on the EM 10 diet is considered as 1, the increases are 1.05, 1.25, 1.41 and 1.59, respectively. These results indicate that renal hypertrophy is slightly greater in the unilaterally nephrectomized rats than in the intact animals. It was found that the total solids of the kidneys of the control groups were practically all between 23 and 26 per cent of the wet weight.

The standard errors for the urea ratio ($\frac{\text{urea excreted in one hour's urine}}{\text{urea in 100 cc. of blood}}$) are comparatively small, although the individual values vary widely. The average values for the intact animals are 47, 58, 60, 64 and 71 for the groups receiving the EM 10, the EM 20, the EM 40, the EM 60 and the EM 80 diet, respectively, whereas the ratios for the unilaterally

TABLE 2—*Observations on Control Animals Fed a Variety of Diets*

Renal Condition and Diet	Value	Duration of Experiment, Days	Surface Area	Blood Pressure, Mm	Heart Weight		Total Solids of Kidneys, Percentage	Twenty Four Hour Urine Concentration Test		Urea Ratio	Nonprotein Nitrogen, Mg per 100 Cc
					Surface Area, > 100, Gm	Weight, X 100, Gm		Volume, Cc	Specific Gravity		
2 kidneys EM 10	Minimum	84	234	116	0.149	0.350	23.3	1.1	1.0230	23	22
	Maximum	175	529	144	0.199	0.625	26.3	3.6	1.0769	71	51
	Average	105 ± 5.7	334 ± 11.4	130	0.167	0.416 ± 0.009	24.5	1.9	1.0500	36 ± 1.45	33
	Rats	28	28	27	28	28	6	13	13	22	15
1 kidney EM 10	Minimum	84	285	118	0.149	0.274		1.4	1.0349	29	23
	Maximum	175	477	144	0.196	0.378		3.3	1.0731	63	61
	Average	118 ± 8.3	379 ± 16.2	133	0.174	0.312 ± 0.009	26.0	2.5	1.0541	49	37
	Rats	12	12	12	12	12	1	8	8	9	10
2 kidneys EM 20	Minimum	87	278	112	0.148	0.328	21.2	1.7	1.0363	28	29
	Maximum	175	500	136	0.192	0.536	26.8	3.1	1.0628	52	53
	Average	106 ± 5.8	343 ± 12.7	125	0.168	0.411 ± 0.013	25.4	3.1	1.0480	37 ± 1.54	39
	Rats	23	23	23	23	23	7	12	11	19	13
1 kidney EM 20	Minimum	84	272	104	0.132	0.262	21.0	0.7	1.0315	20	26
	Maximum	175	462	146	0.188	0.405	27.3	5.4	1.0784	61	45
	Average	116 ± 5.9	356 ± 10.4	127	0.161	0.328 ± 0.009	24.6	2.7	1.0562	36 ± 0.89	34
	Rats	23	23	23	23	23	13	20	19	19	8
2 kidneys EM 40	Minimum	87	260	112	0.131	0.386	24.4	0.6	1.0402	24	33
	Maximum	175	446	140	0.181	0.609	26.4	4.4	1.0828	45	61
	Average	111 ± 4.5	327 ± 10.4	122	0.159	0.491 ± 0.011	25.6	2.0	1.0601	37 ± 1.11	42
	Rats	27	27	27	27	27	11	17	17	25	14
1 kidney EM 40	Minimum	87	262	110	0.137	0.384	24.3	1.3	1.0510	28	35
	Maximum	175	442	133	0.180	0.520	26.2	1.9	1.0713	51	59
	Average	117 ± 8.0	366 ± 12.5	125	0.161	0.397 ± 0.016	25.1	2.9	1.0612	36 ± 0.84	44
	Rats	17	17	17	17	17	5	11	11	17	12
2 kidneys EM 60	Minimum	75	265	114	0.133	0.435	24.2	1.4	1.0442	41	35
	Maximum	175	511	142	0.185	0.630	26.4	4.5	1.0795	50	70
	Average	113 ± 6.5	332 ± 11.3	128	0.156	0.423 ± 0.012	25.1	2.6	1.0598	38 ± 1.21	45
	Rats	26	26	26	26	26	10	16	16	22	14
1 kidney EM 60	Minimum	89	265	120	0.145	0.364	23.7	1.6	1.0300	42	48
	Maximum	182	437	148	0.188	0.575	24.2	5.5	1.0825	59	71
	Average	117 ± 6.7	364 ± 10.0	133	0.163	0.441 ± 0.010	23.9	3.2	1.0516	33 ± 0.90	54
	Rats	16	16	16	16	16	4	10	10	12	8
2 kidneys EM 80	Minimum	89	276	114	0.149	0.460	22.4	0.7	1.0278	22	32
	Maximum	185	467	144	0.212	0.775	25.6	4.7	1.0691	45	62
	Average	123 ± 4.8	348 ± 7.7	127	0.170	0.627 ± 0.016	24.0	2.8	1.0501	32 ± 1.00	42
	Rats	44	44	44	44	44	22	22	22	30	11
1 kidney EM 80	Minimum	88	240	110	0.125	0.340	22.0	3.1	1.0405	21	38
	Maximum	185	437	140	0.183	0.691	24.6	4.8	1.0585	43	74
	Average	116 ± 7.1	333 ± 9.6	126	0.158	0.466 ± 0.022	23.2	3.8	1.0464	29 ± 0.99	59
	Rats	22	22	21	21	22	13	5	5	13	8

* Average and standard error for control animals on a specific diet

nephrectomized animals on the same diets are 48, 42, 49, 49 and 49. The ratios for the unilaterally nephrectomized rats appear to be remarkably constant regardless of diet, indicating perhaps less flexibility of renal function.

Increases of the kidney weights and urea ratios for the intact rats are strikingly proportional, as shown by the constancy of the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios of 36, 37, 37, 38 and 32 for the rats on the EM 10, the EM 20, the EM 40, the EM 60 and the EM 80 diet, respectively, whereas the varied ratios for the unilaterally nephrectomized rats on these diets are 40, 36, 36, 33 and 29, respectively. The ratios for the intact rats are constant, but there is a decrease in the values for the unilaterally nephrectomized rats.

In general, there appears to be little difference in the urinary volumes or specific gravities of the urines obtained during a concentration test for the intact and the unilaterally nephrectomized rats on the various diets. The majority of the urinary volumes were between 1 and 3 cc, and most of the specific gravities were between 1.0500 and 1.0600.

The nonprotein nitrogen concentration of the blood plasma of all intact rats remained fairly constant. There was little difference in these values for the intact and the unilaterally nephrectomized animals on the first three diets. The unilaterally nephrectomized rats on the EM 60 and the EM 80 diet showed values distinctly higher than those for the corresponding intact animals.

On the basis of the foregoing results, the following values have been taken as the limits of normal: blood pressures below 140 mm of mercury, urinary volumes below 5 cc, urinary specific gravities above 1.0400, urinary protein content below 0.05 Gm and urea ratios above 30.

Partially Nephrectomized Rats—The data for partially nephrectomized rats in good health on diets EM 10, EM 20, EM 40, EM 60 and EM 80 are shown in tables 3 to 7. Charts 1 to 8 were prepared to facilitate comparisons of the effects of the various diets on the blood pressure, the total solids of the kidneys, in relation to surface area, the urinary volume, the specific gravity and urinary protein as determined by the concentration test and the urea ratio and its relation to the urea in the blood and the urine.

Blood Pressure The effects of the diets on blood pressure are summarized in chart 1. The percentage of animals with blood pressures above the upper limits of normal (140 mm) was greatest in the groups receiving the EM 40 and the EM 60 diet. However, the percentage of animals with pressures above 180 mm was about the same in the groups fed the first four diets and appreciably less in the group fed the EM 80 diet. It is of interest that on further analysis (not in the chart) the percentage incidence of blood pressures above 200 mm was

TABLE 3—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 10 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Kidney Total Solids, %	Twenty Four Hour Urine Concentration Test			Urea Ratio	Non protein Nitrogen, Mg per 100 Cc
				Surface Area × 100	Surface Area × 100		Volume, Cc	Specific Gravity	Albumin, Gm		
1	75	307	154	0 181	0 194		5 0	1 0297	0 041	11	72
2	75	306	156	0 175	0 237		3 8	1 0259		15	64
3	75	289	150	0 173	0 209		4 5	1 0277	0 007	13	75
4	75	242	212	0 208	0 126		7 3	1 0203	0 056	8	87
5	77	260	128	0 193	0 276		6 0	1 0325	0 017	19	49
6	77	266	126	0 184	0 202		3 8	1 0359		20	61
7	77	258	138	0 174	0 230		3 7	1 0391		20	42
8	77	275	156	0 234	0 237		12 7	1 0222	0 085	19	53
9	77	356	136	0 188	0 232		5 7	1 0381	0 007	34	50
10	84	339	182	0 198	0 151		10 7	1 0177	0 067	15	72
11	84	272	218	0 244	0 258		5 5	1 0315	0 107	17	
12	85	350		0 186	0 228		3 5	1 0433		22	54
13	85	322			0 208		4 0	1 0398	0 005	25	
14	85	330	176	0 206	0 245		6 8	1 0333	0 048	18	43
15	85	356	160	0 181	0 245		8 2	1 0316	0 096	24	40
16	85	302	160	0 200	0 239		7 3	1 0285	0 038	23	32
17	85	348	196	0 237	0 289		9 0	1 0350	0 197	16	50
18	85	289	160	0 205	0 235		5 6	1 0315	0 055	17	46
19	89	238	210	0 229	0 220		6 0	1 0217	0 040		76
20	89	323	152	0 186	0 224		4 0	1 0315		18	57
21	89	262	206	0 192	0 246		2 9	1 0535		10	72
22	89	320	104	0 169	0 203		4 0	1 0319		16	63
23	102	297	192	0 211	0 223		8 8	1 0189	0 041		64
24	107	278	130	0 110	0 227	23 8	4 8	1 0240	0 003	17	
25	107	230	124	0 148	0 191	21 6	3 1	1 0210	0 001	11	
26	107	260	156	0 189	0 259	19 3	5 9	1 0271	0 038	13	
27	107	220	136	0 168	0 237	20 6	3 1	1 0322		9	
28	107	308	172	0 174	0 283	20 2	3 3	1 0291		11	67
29	107	304	136	0 171	0 198	23 0	3 4	1 0328		20	40
30	107	244	152	0 197	0 231	20 0	4 1	1 0213		8	68
31	107	258	134	0 152	0 276	22 0	1 7	1 0484		18	55
32	107	230	156	0 162	0 223	21 8	2 0	1 0383		13	46
33	107	232			0 244	24 2	3 8	1 0314		15	
34	109	355	128	0 179	0 221		4 1	1 0327	0 033		61
35	109	280	188	0 164	0 223		2 9	1 0359		16	61
36	110	280	184	0 228	0 272	19 8	6 7	1 0235	0 063	12	
37	110	230	160	0 173	0 218	19 8	5 4	1 0227	0 007	8	
38	110	222	160	0 229	0 158	16 8	8 7	1 0135	0 010	3	
39	110	196	250	0 229	0 139	18 0	6 3	1 0173	0 017		
40	114	276	164	0 214	0 338	19 4	1 5	1 0298	0 044	14	75
41	114	254	230	0 217	0 310	16 5	7 0	1 0202		5	84
42	114	341	146	0 206	0 239	19 7	4 8	1 0311	0 018	11	83
43	114	308	164	0 192	0 227	22 1	8 7	1 0207	0 037	10	80
44	114	313	214	0 256	0 256	19 8	5 7	1 0311	0 097	7	
45	114	326	174	0 222	0 201	20 2	7 6	1 0358	0 209	7	75
46	114	235	192	0 250	0 338	17 3	6 7	1 0311	0 167	10	96
47	114	302	166	0 197	0 270	17 0	7 0	1 0258	0 029	11	76
48	114	301	132	0 202	0 320	22 0	3 7	1 0386		15	69
49	116	216	216	0 219	0 165	15 7	4 5	1 0149	0 025	3	
50	116	299	144	0 159	0 208	23 0	5 7	1 0172	0 021	9	
51	116	274	202	0 192	0 206	19 0	7 8	1 0227	0 088	6	
52	116	250	160	0 200	0 170	18 3	5 8	1 0167	0 007	4	
53	116	283	184	0 222	0 213	18 4	5 2	1 0235	0 010	5	
54	116	276	140	0 178	0 165	22 4	5 3	1 0257	0 008	11	
55	116	230	164	0 212	0 251	19 2	8 1	1 0220	0 034	12	
56	116	270	160	0 165	0 236	20 8	2 6	1 0340		15	
57	116	254	134	0 179	0 222	23 9	2 5	1 0481		21	
58	116	252	170	0 249	0 172	18 4	9 9	1 0201	0 085	8	
59	133	354	156	0 183	0 196		8 8	1 0194	0 041		63
60	133	270	162	0 182	0 228		4 7	1 0333	0 110		61
61	136	334	142	0 188	0 172		14 5	1 0184	0 070		56
62	136	285	128	0 166	0 253		2 9	1 0370			46
63	158	376	186	0 212	0 271		12 5	1 0218		12	61

TABLE 4—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Kidney Total Solids, %	Twenty Four Hour Urine Concentration Test			Urea Ratio	Non protein Nitrogen, Mg per 100 Cc
				Surface Area / 100	Surface Area × 100		Volume, Cc	Specific Gravity	Albumin, Gm		
1	75	286	116	0.164	0.264		5.3	1.0297	0.041		59
2	90	212	122	0.167	0.289		4.0	1.0313			
3	90	379	138	0.172	0.256		9.3	1.0262	0.086		55
4	90	306	138	0.167	0.268		5.3	1.0113	0.101		70
5	90	295	152	0.170	0.236		3.5	1.0353			51
6	90	306	128	0.162	0.218		5.0	1.0309	0.041		67
7	103	376	158	0.186	0.396						118
8	103	313	138	0.200	0.363		17.1	1.0176	0.280		82
9	103	314	124	0.161	0.246		8.5	1.0232	0.065		72
10	103	419	226	0.229	0.455		15.7	1.0204	0.297		123
11	104	421	194	0.206	0.416		11.5	1.0210	0.155		129
12	107	283	152	0.174	0.215	21.4	5.0	1.0343		5	111
13	107	307	124	0.152	0.237	23.4	7.5	1.0311	0.005	19	
14	107	314	154	0.199	0.296	18.3	14.5	1.0168	0.032	6	101
15	107	240	196	0.190	0.355	15.5	9.0	1.0179	0.060	4	
16	107	318	182	0.216	0.333	15.1	10.0	1.0196	0.013	5	108
17	107	230	156	0.144	0.240	21.6	1.1	1.0476		12	69
18	107	376	156	0.171	0.278	20.1	7.3	1.0268	0.035		87
19	107	308	174	0.183	0.259	19.3	6.8	1.0209	0.039	9	87
20	107	364	132	0.190	0.241	22.0	7.8	1.0251	0.035	9	82
21	107	356	156	0.175	0.241	23.2	3.9	1.0366		23	58
22	107	268	138	0.135	0.298	20.4	4.0	1.0344	0.009	12	74
23	107	265	150	0.164	0.295	18.2	6.7	1.0261	0.071	12	90
24	107	304	134	0.175	0.273	19.8	8.9	1.0224	0.065	6	83
25	107	250	124	0.137	0.275	18.0	4.5	1.0257	0.008	14	69
26	107	272	130	0.172	0.318	19.2	6.0	1.0324	0.100	16	125
27	107	234	198	0.234	0.192	16.4	8.6	1.0148	0.034	3	117
28	107	250	138	0.190	0.382	18.3				15	105
29	107	248	208	0.294	0.413	14.1				5	125
30	119	323	150	0.189	0.252	20.1	12.3	1.0206	0.036	10	
31	119	355	166	0.230	0.370	13.9	22.8	1.0138	0.078	6	
32	119	299	188	0.230	0.313	16.2	12.2	1.0230	0.145	12	
33	119	318	212	0.222	0.188	16.2	19.4	1.0124	0.051	6	
34	119	275	176	0.217	0.358	15.8	15.0	1.0175	0.163	8	
35	120	265	220	0.265	0.757	16.5	13.2	1.0167	0.153	5	
36	120	299	148	0.192	0.307	18.8	7.9	1.0258	0.103	11	
37	120	323	136	0.166	0.242	22.9	5.9	1.0308		17	
38	120	315	180	0.194	0.317	18.7	11.4	1.0248	0.146	10	
39	120	330	134	0.179	0.205	23.0	6.6	1.0270	0.040	12	
40	120	306	116	0.188	0.301	20.5	6.0	1.0326	0.064	21	
41	120	265	132	0.150	0.201	21.9	4.6	1.0180	0.002	16	
42	120	283	138	0.165	0.222	22.9	7.1	1.0248	0.024	16	
43	120	274	160	0.155	0.244	20.0	5.8	1.0188	0.052	12	
44	134	411	164	0.222	0.602		17.1	1.0192	0.204		89
45	134	421	138	0.169	0.249		5.2	1.0373	0.079		54
46	134	425	130	0.180	0.216		8.2	1.0291	0.042		
47	134	362	138	0.164	0.267		8.5	1.0207	0.089		
48	134	370	156	0.183	0.310		17.1	1.0146	0.120		83
49	134	386	184	0.203	0.196		16.5	1.0139	0.046		97
50	134	265	196	0.226	0.332		7.7	1.0207	0.158		97
51	134	402	204	0.196	0.565		9.5	1.0260	0.250		64
52	134	366	174	0.292	0.269		15.3	1.0153	0.141		100
53	164	334	168	0.162	0.266		6.7	1.0274		11	110
54	164	310	190	0.186	0.298		12.0	1.0255		8	108
55	164	275	144	0.255	0.323		11.8	1.0189		3	133
56	164	389	230	0.246	0.391		5.5	1.0144		6	129
57	175	452	128	0.179	0.276		10.7	1.0299			58
58	175	439	188	0.214	0.476		24.0	1.0166	0.312	6	
59	175	324	166	0.190	0.450		12.2	1.0223	0.208	12	74

as follows EM 10, 15, EM 20, 10, EM 40, 6, EM 60, 0, and EM 80, 1
The highest blood pressure in this series (250 mm) was obtained in a rat on the EM 10 diet

TABLE 5—Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 per Cent Dried Extracted Beef Muscle

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test				Urea Ratio	Non protein Nitrogen, Mg per 100 Cc
				Surface Area × 100	Surface Area × 100	Kidney Total Solids, %	Volume, Cc	Specific Gravity	Albumin, Gm		
1	75	306	154	0 186	0 311		9 5	1 0248	0 062	13	91
2	75	334	146	0 198	0 240		21 4	1 0173	0 192	9	131
3	75	295	142	0 187	0 376		7 1	1 0330	0 094	15	85
4	75	270	170	0 196	0 205		11 7	1 0181	0 053	7	155
5	75	306	174	0 194	0 368		11 1	1 0236	0 093	12	111
6	111	306	144	0 162	0 862		4 9	1 0390	0 080	17	
7	113	320	136	0 172	0 437	16 8	13 6	1 0167			150
8	113	250	164	0 188	0 280	18 8	9 8	1 0190	0 094	5	
9	113	328	138	0 171	0 420	16 7	15 6	1 0180	0 111		129
10	113	278			0 437	14 4	13 7	1 0125	0 056		
11	113	302	182	0 187	0 380	14 4	17 0	1 0129	0 070	5	200
12	113	306	178	0 165	0 480	17 2	5 4	1 0249	0 048	14	121
13	113	248	128	0 153	0 265	17 2	5 7	1 0235	0 018	13	111
14	113	295	156	0 171	0 422	16 5	6 7	1 0249	0 046		114
15	113	372	162	0 199	0 375	17 9	18 5	1 0197	0 220	14	166
16	113	252	134	0 153	0 366	18 5	7 5	1 0249	0 061	15	
17	113	254	162	0 187	0 272	19 1	7 2	1 0203	0 036	9	
18	113	336	158	0 191	0 321	17 5	11 0	1 0166	0 023	12	132
19	118	268			0 314	18 4	10 7	1 0192	0 017	11	
20	118	310	138	0 176	0 360	18 4	13 9	1 0195	0 070	3	
21	118	254	144	0 163	0 370	18 7	8 6	1 0241	0 053	4	
22	118	246	166	0 172	0 412	18 9	6 5	1 0272	0 056	11	
23	118	260	184	0 186	0 370	19 8	8 1	1 0220	0 050	9	
24	118	341	158	0 195	0 386	19 2	11 1	1 0239	0 095	11	
25	118	276	192	0 184	0 444	14 1	12 1	1 0173	0 050	4	
26	118	318	210	0 212	0 428	14 7	15 5	1 0143	0 073	4	
27	120	320	144	0 164	0 336	17 1	14 0	1 0195	0 069		
28	120	238	176	0 170	0 538	12 6	13 6	1 0139	0 075		
29	120	341	186	0 186	0 548	13 0	19 8	1 0162	0 131	8	
30	120	314	162	0 167	0 322	18 0	17 1	1 0165	0 060	4	
31	120	250	138	0 196	0 326	18 3	11 2	1 0215	0 057	10	
32	120	283	156	0 216	0 371	15 2	17 3	1 0161	0 208		
33	127	364	168	0 183	0 415		18 3	1 0159	0 147		151
34	127	364	182	0 215	0 361		21 0	1 0137	0 126		184
35	127	307	148	0 174	0 370		10 0	1 0212	0 134		113
36	127	313	126	0 170	0 480		10 4	1 0228	0 210		150
37	127	373	190	0 240			20 8	1 0144	0 227		272
38	127	343	176	0 236	0 260		21 0	1 0129	0 080		272
39	139	310	172	0 196	0 538		17 7	1 0197		11	172
40	139	386	186	0 200	0 728		22 7	1 0180		9	200
41	146	334	162	0 156	0 326		13 4	1 0178	0 108	13	
42	146	268	166	0 202	0 382		10 8	1 0189	0 202	2	370
43	146	323	216	0 196	0 460		17 6	1 0215	0 338	11	180
44	146	341	166	0 214	0 436		16 2	1 0210		10	148
45	148	326	146	0 190	0 410		15 2	1 0202	0 221	12	196
46	148	370	152	0 189	0 340		19 5	1 0202	0 238	13	125
47	148	291	182	0 171	0 610		16 9	1 0148	0 120	5	
48	148	280	176	0 190	0 440		11 3	1 0183	0 212	11	155
49	148	254	224	0 236	0 228		15 6	1 0166	0 152	2	387
50	173	348	144	0 193	0 289		18 6	1 0180		15	133
51	173	313	126	0 145	0 296						53

The correlation coefficients and probable errors were calculated for blood pressure and $\frac{H}{S} \frac{W}{A}$ ratios for each diet as follows EM 10, 0.67 ± 0.05 , EM 20, 0.52 ± 0.06 , EM 40, 0.60 ± 0.06 , EM 60, 0.14 ± 0.10 , and EM 80, 0.33 ± 0.07 These results for the partially neph-

rectomized animals show a substantial relation for the first three diets and a negligible relation for the EM 60 diet and a slight relation for the EM 80 diet

TABLE 6—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 60 per Cent Dried Extracted Beef Muscle*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Twenty Four Hour Urine Concentration Test				Urea Ratio	Non protein Nitrogen, Mg per 100 Cc
				Surface Area $\times 100$	Surface Area $\times 100$	Kidney Total Solids, %	Volume, Cc	Specific Gravity	Albumin, Gm		
1	75	348	144	0 210	0 520		10 8	1 0268	0 052	25	133
2	75	333	144	0 212	0 413		17 8	1 0155	0 107	12	231
3	75	232	166	0 168	0 354		9 5	1 0156	0 062	8	250
4	75	306	142	0 160	0 401		8 5	1 0238	0 070	11	113
5	103	220			0 317	17 1	8 1	1 0206		6	
6	103	278	146	0 161	0 102	18 3	6 5	1 0275	0 040	20	
7	103	252	192	0 162	0 495	14 5	7 4	1 0223	0 069	12	
8	103	256	196	0 157	0 558	13 1	11 3	1 0207	0 190	8	
9	103	295	172	0 166	0 467	13 1	16 8	1 0170	0 096	13	
10	103	258	172	0 161	0 437	15 7	10 6	1 0162	0 042	14	
11	103	299	180	0 185	0 550	16 8	10 3	1 0219		15	
12	103	304	176	0 188	0 652	13 7	12 5	1 0176	0 118	6	
13	103	272	174	0 152	0 468	16 3	8 0	1 0211	0 089	8	
14	104	379	126	0 190	0 394		7 8	1 0323	0 095	29	126
15	104	299	134	0 184	0 396		9 0	1 0256	0 180	13	177
16	104	334	126	0 165	0 260		15 0	1 0191	0 044	16	149
17	104	280	124	0 169	0 330		3 7	1 0421		28	
18	104	280	124	0 180	0 362		8 4	1 0261	0 070	16	149
19	104	341	138	0 173	0 382		11 4	1 0237	0 102	17	177
20	105	240	190	0 177	0 550		8 2	1 0177	0 090	28	150
21	105	242	182	0 212	0 545		9 5	1 0186	0 222	22	333
22	108	292	136	0 174	0 226		11 3	1 0244	0 320		
23	113	241	154	0 189	0 376		11 4	1 0188	0 123	7	192
24	113	238	156	0 155	0 340		6 3	1 0300	0 058	10	142
25	113	302	124	0 145	0 338		12 5	1 0236	0 162	17	152
26	113	203	196	0 238	0 412		10 8	1 0156	0 122	2	393
27	113	244	142	0 195	0 347		10 2	1 0209	0 145	7	201
28	113	220	176	0 168	0 525		11 3	1 0158	0 092	3	288
29	113	310	154	0 164	0 394		12 6	1 0163	0 103	13	152
30	118	280	176	0 168	0 496		9 2	1 0207	0 048	11	110
31	118	276	184	0 176	0 366		12 5	1 0195	0 104	8	133
32	118	274	142	0 167	0 392		14 7	1 0168	0 077	5	210
33	118	314	146	0 187	0 487		15 8	1 0215	0 174		160
34	118	268	166	0 164	0 505		5 6	1 0378	0 071	22	170
35	118	299	142	0 174	0 370		8 9	1 0270	0 062	11	144
36	118	302	142	0 174	0 456		15 3	1 0191		10	210
37	118	254	176	0 173	0 400	18 7	10 2	1 0189	0 090	10	
38	118	278	160	0 173	0 480	18 4	11 9	1 0188	0 116	11	152
39	120	358	158	0 181	0 421		17 3	1 0203	0 166		150
40	134	334	154	0 209	0 428		20 0	1 0179	0 168		326
41	136	328	180	0 230	0 707		18 0	1 0137	0 061		100
42	136	345	182	0 229	0 417		17 7	1 0158	0 147		90
43	136	348	158	0 189			6 7	1 0230	0 008		80
44	151	268	152	0 177	0 322		12 1	1 0151	0 151	7	570
45	151	248	150	0 135	0 252		10 8	1 0142	0 092		260
46	151	256	182	0 165	0 333		6 8	1 0183	0 059	6	
47	175	278	186	0 186	0 781		14 0	1 0149	0 190	3	324
48	175	310	184	0 199	0 503		15 2	1 0162	0 117	2	340

Kidneys The data for total solids of the kidney remnants expressed in milligrams per hundred square centimeters of surface area are presented in chart 2, and the average values are as follows 47 ± 18 , 52 ± 13 , 65 ± 17 , 70 ± 24 , and 79 ± 16 for the groups fed the FM 10 the EM 20, the EM 40, the EM 60 and the EM 80 diet.

TABLE 7—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 80 per Cent Dried Extracted Beef Muscle*

Rat	Dura- tion of Experi- ment, Days	Surface Area, Sq Cm	Blood Pres- sure, Mm	Heart Weight	Kidney Weight	Twenty Hour Urine Concentration Test				Urea Ratio	Non protein Nitro- gen, Mg per 100 Gc
				Surface Area × 100	Surface Area × 100	Kidney Total Solids, %	Vol- ume, Cc	Specific Gravity	Albu- min, Gm		
1	88	304	116	0 161	0 430						56
2	100	286	148	0 165	0 675	15 2	8 8	1 0216		16	
3	100	283	124	0 143	0 500	16 3	5 8	1 0251	0 008	19	170
4	100	207	152	0 157	0 374	18 5	8 0	1 0182	0 037	10	
5	100	260	136	0 154	0 592	15 2	9 0	1 0187	0 005	11	190
6	100	207	188	0 160	0 543	15 8	5 1	1 0208	0 041	6	
7	100	275	146	0 159	0 570	15 5	14 1	1 0163	0 109	12	240
8	102	228	202	0 215	0 835					6	
9	102	265	160	0 162	0 526					18	
10	102	248	138	0 153	0 515					15	
11	102	266	190	0 190	0 516					18	
12	102	276	118	0 161	0 484					25	
13	102	212	166	0 156	0 470					18	
14	107	232	190	0 190	0 585	12 5	12 1	1 0141	0 061	5	400
15	107	234	148	0 151	0 603	17 0	16 6	1 0182	0 156		
16	107	205	156	0 158	0 530	18 4	17 5	1 0162	0 128		
17	107	270	138	0 149	0 400	18 2	13 6	1 0225	0 216	13	128
18	107	207	134	0 145	0 380	18 8	7 5	1 0158	0 017		
19	107	217	132	0 137	0 346	19 7	6 0	1 0228	0 032	14	
20	107	228	152	0 147	0 435	16 0	6 7	1 0238	0 106	10	
21	108	301	148	0 181	0 562	15 6	13 1	1 0172	0 121	9	200
22	108	234	168	0 171	0 515	16 5	7 1	1 0181	0 054	12	
23	108	254	150	0 140	0 502	15 6	8 7	1 0175	0 120	9	
24	108	274	144	0 169	0 546	15 7	12 3	1 0156		13	148
25	108	297	148	0 169	0 608	13 1	14 0	1 0167	0 106		300
26	108	252	102	0 119	0 577	15 4	7 2	1 0225	0 112	20	212
27	108	230	158	0 173	0 377	18 8	7 2	1 0228	0 096	18	
28	108	228	134	0 169	0 462	20 0	4 7	1 0291	0 018	17	
29	108	203	186	0 201	0 508	13 5	10 1	1 0112	0 020	5	
30	108	246	158	0 185	0 510	14 8	11 0	1 0178	0 134	9	
31	108	258	158	0 208	0 656	13 1	14 9	1 0152	0 107	6	400
32	108	266	168	0 149	0 487	16 7	9 1	1 0216		19	260
33	108	228	142	0 153	0 300	17 4	7 5	1 0217	0 051	15	
34	108	250	138	0 155	0 460	19 6	8 5	1 0276	0 113		91
35	109	250	136	0 172	0 450		6 3	1 0305	0 080	14	136
36	109	265	126	0 157	0 379		6 8	1 0297	0 008	15	111
37	109	274	136	0 174	0 440		11 5	1 0199	0 052	13	125
38	109	256	160	0 184	0 577		10 7	1 0180	0 153	7	252
39	109	301	124	0 147	0 434		5 9	1 0356	0 021	19	111
40	109	302	142	0 182	0 601		13 2	1 0196	0 100		154
41	109	231	192	0 228	0 686					7	
42	109	320	192	0 201	0 765						
43	109	270	138	0 156	0 470					14	
44	109	242	178	0 172	0 586					14	
45	109	216	152	0 192	0 174					8	
46	109	252	164	0 181	0 470					13	
47	109	328	134	0 150	0 197					33	
48	110	291	138	0 216	0 412		17 6	1 0156	0 091		148
49	110	262	158	0 183	0 166		11 1	1 0152	0 092	7	167
50	110	230	138	0 168	0 417		4 3	1 0337	0 062	10	
51	110	242	126	0 158	0 322		4 9	1 0317	0 029		
52	110	265	146	0 156	0 398		7 7	1 0231	0 097	12	133
53	110	302	132	0 174	0 837		18 9	1 0180	0 185	17	136
54	111	234	162	0 185	0 336	16 3	11 5	1 0150	0 039	10	
55	111	301	142	0 200	0 547	14 3	13 3	1 0191	0 080	19	200
56	111	295	156	0 211	0 605	14 7	16 6	1 0182	0 156	17	216
57	111	283	156	0 203	0 580	15 2	17 5	1 0162	0 128		288
58	111	205	146	0 116	0 460	16 9	8 9	1 0203	0 141	11	
59	111	250	138	0 177	0 508	15 1				10	270
60	111	231	168	0 163	0 465	15 9				11	
61	111	231	168	0 183	0 623	14 6				12	
62	111	226	158	0 155	0 502	14 9				8	
63	119	286	122	0 179	0 340						
64	123	272	166	0 202	0 749		8 3	1 0207			
65	127	314	158	0 229	0 505		11 0	1 0210	0 125		154
66	132	238	124	0 215	0 384						
67	133	302	170	0 220	0 732		13 2	1 0177	0 152		258
68	140	292	172	0 210	0 738		9 2	1 0217	0 127		285
69	140	292	144	0 180	0 513		4 8	1 0353	0 028		125
70	140	284	150	0 197	0 820		10 1	1 0176	0 117		278
71	140	274	158	0 182	0 640		8 5	1 0193			192
72	142	292	142	0 203	0 737		14 1	1 0207	0 272		160
73	147	289	146	0 245			20 3	1 0139	0 183		400
74	147	252	182	0 212	0 793		12 0	1 0166	0 121		266
75	154	362	176	0 234	0 498						
76	154	268	170	0 183	0 497						
77	155	340	160	0 222	0 563		12 4	1 0219	0 150		190
78	155	283	165	0 191	0 490		6 8	1 0311	0 104		110
79	155	341	190	0 338	0 865		25 8	1 0153	0 289		307
80	171	314	196	0 214	0 518		8 0	1 0202	0 159		183
81	171	318	174	0 240	0 573		9 1	1 0207	0 091		308

respectively. If the average value for the group fed the EM 10 diet is considered as 1, the ratios for those fed the respective diets are 1.0, 1.11, 1.38, 1.49 and 1.68, representing a proportional increase. These ratios are quite comparable to figures obtained for the unilaterally nephrectomized rats and to a lesser extent for the intact rats.

Nonprotein Nitrogen. Retention of nitrogen in the blood seems to vary with the intake of protein. The average values in milligrams of nonprotein nitrogen of plasma for each diet are as follows: EM 10, 61; EM 20, 90; EM 40, 165; EM 60, 202; and EM 80, 199. These values are all much higher than those obtained for the control groups.

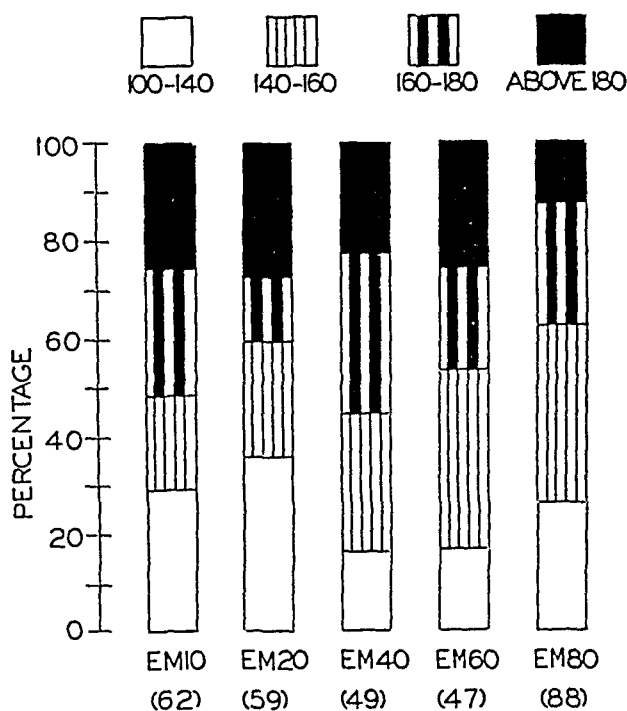


Chart 1—Effect of diet on the blood pressure of partially nephrectomized rats. In this chart and in similar charts the figures in parentheses represent the number of animals.

on similar diets. There were marked individual variations as shown in the tables for the respective diets.

RENAL FUNCTION

Urine Concentration Test.—The effect of various diets on the urinary volume is shown in chart 3. It is seen that there is a marked progressive increase in the incidence and degree of polyuria with the first three diets. Forty-two per cent of the animals on the EM 40 diet excreted over 15 cc of urine which represents the greatest degree of polyuria in these experiments. In view of the small amount of urine excreted by the control rats these results indicate a marked

disturbance in the factors concerned in the retention or reabsorption of water in the kidney

Chart 4 shows the effect of diet on the specific gravity of the urine after correction for the effect of proteinuria. It is noted that there is a progressive increase in the percentage of animals having low specific gravities in groups fed the EM 10, the EM 20 and the EM 40 diet. The marked preponderance of specific gravities between 1.0100 and 1.0200 tends to reflect the large amounts of water lost by these animals.

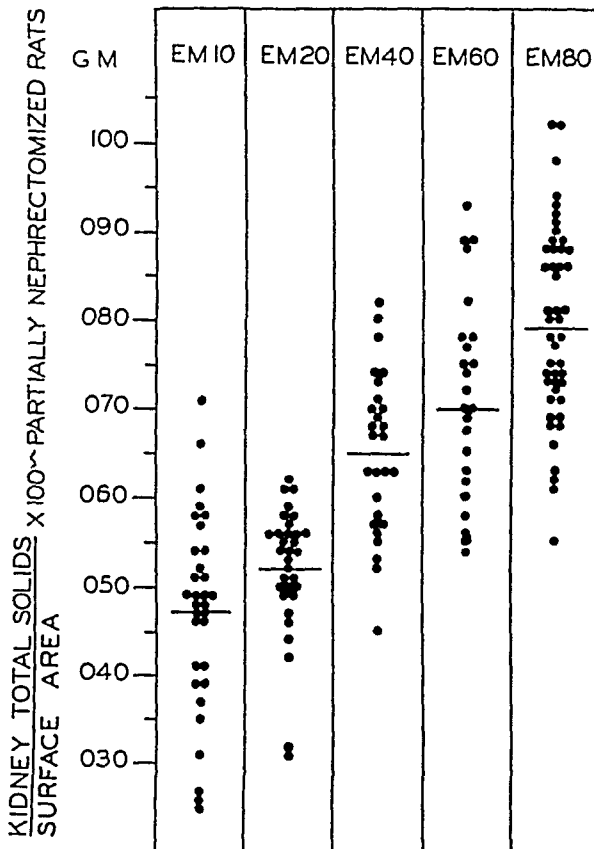


Chart 2—Effect of diet on the total solids of the kidneys per hundred square centimeters of surface area of partially nephrectomized rats

Chart 5 summarizes the effect of diet on the excretion of protein. The greatest output of protein was noted in the group fed the EM 40 diet. The percentage incidence of animals excreting more than 0.2 Gm. of protein daily was about the same for the groups fed the EM 10, the EM 60 and the EM 80 diet. The amount of dietary protein does not appear to be related to the degree of proteinuria.

It is interesting to note that the maximal change in urinary volume, specific gravity and proteinuria was attained with the EM 40 diet. There seems to be no relation between the retention of nitrogen or the

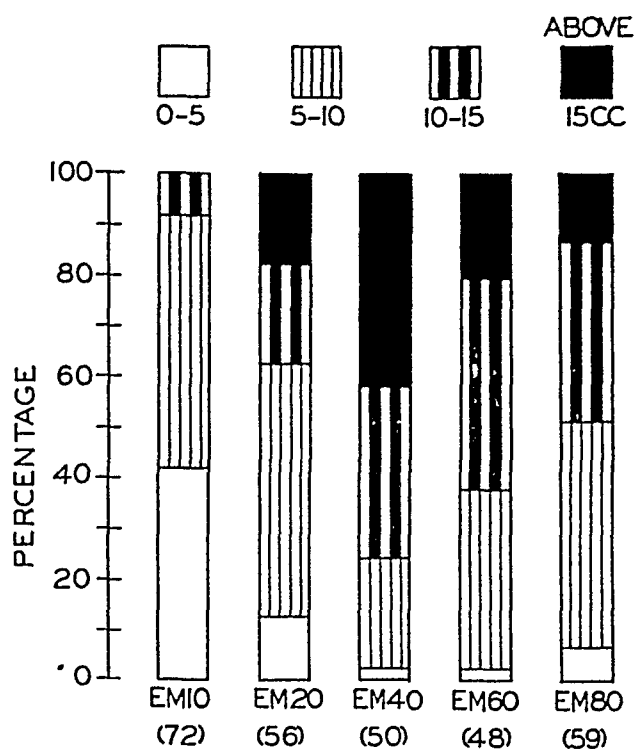


Chart 3—Effect of diet on the urinary volume of partially nephrectomized rats

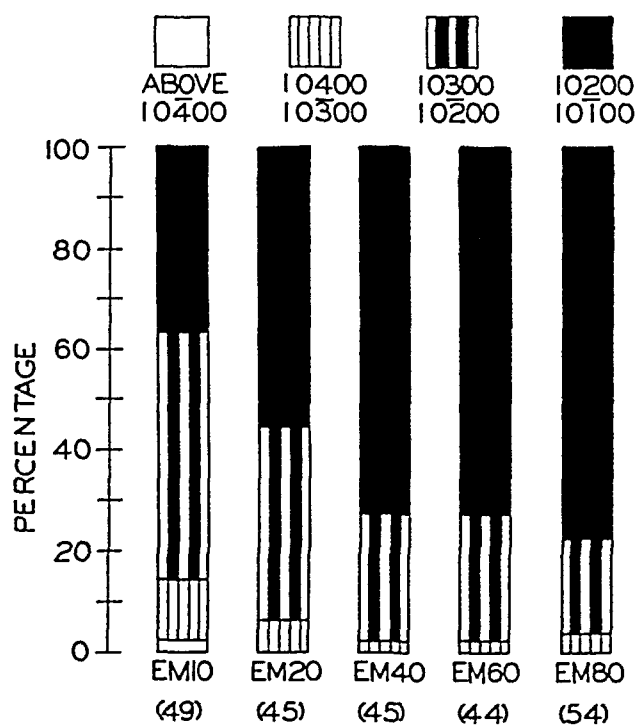


Chart 4—Effect of diet on the specific gravity (after correction for protein) of the urine of partially nephrectomized rats

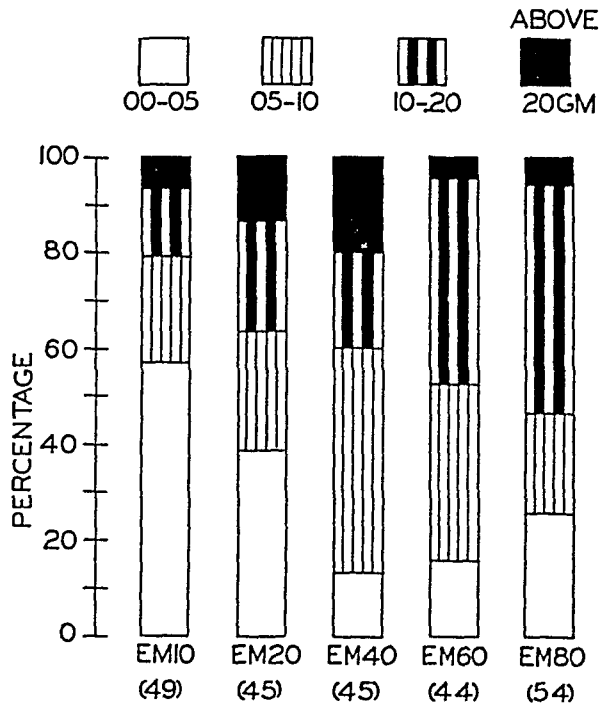


Chart 5—Effect of diet on the excretion of protein of the partially nephrectomized rat

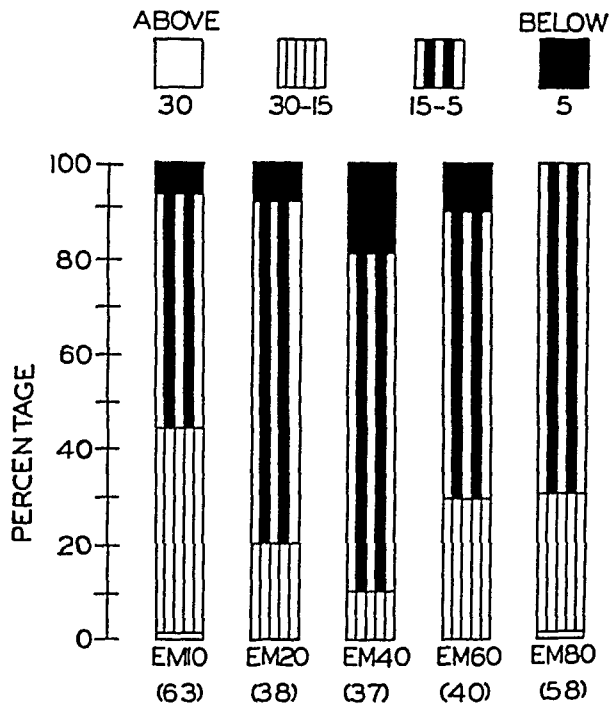


Chart 6—Effect of diet on the urea ratio of the partially nephrectomized rat

degree of hypertension and the renal function as measured by the concentration test

The distribution of the urea ratio values is shown in chart 6. The animals ingesting the EM 40 diet had the largest percentage of ratios below 5. In the dietary group consuming the largest percentage of extracted beef, there was the smallest incidence of animals with renal insufficiency, as judged by the urea ratio.

Effect of Diet on the Urea in the Blood and the Urine—The adjusted curves and their formulas, obtained by procedures previously described,² showing the effect of extracted meat diets on the amount of urea in the blood and the urine in relation to the urea ratio of partially nephrectomized and of control rats are shown in chart 7.

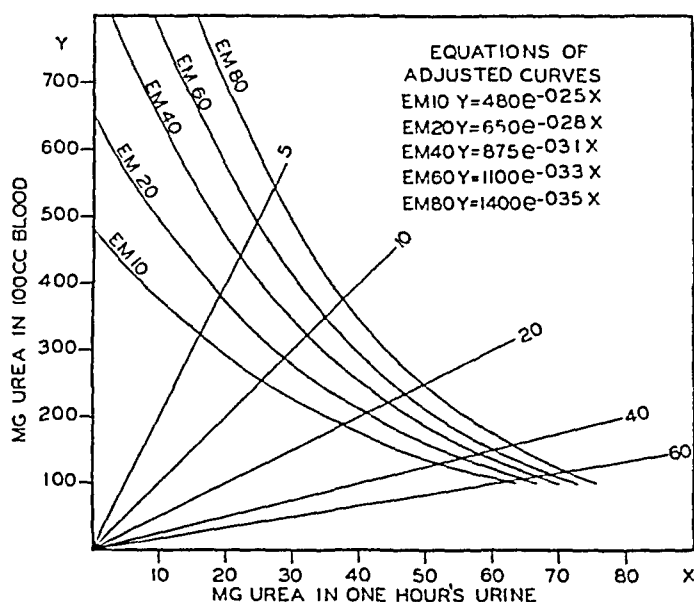


Chart 7—Relation of the adjusted curves for the urea in the blood and the urine

In these experiments the unadjusted and adjusted curves are practically identical for all dietary groups.

When the concentrations of the urea in the blood and the urine are compared at any given urea ratio, the influence of diet is strikingly shown. Since urea is given by mouth in definite amounts for the determination of the urea ratio, it is obvious that the retention of urea in marked renal insufficiency represents a cumulative effect of ingested and metabolic urea. It has been frequently noted that animals die shortly after the urea clearance test if the blood urea exceeds 800 mg of urea per hundred cubic centimeters of blood.

² Ludwig, S., Williams, E. T. R., and Chanutin, A. Experimental Renal Insufficiency Produced by Partial Nephrectomy. VII. The Relationship of Urine Urea, Blood Urea and Urea (Addis) Ratio in Rats on Whole Dried Meat Diets, Arch Int Med 58:89 (July) 1936.

An analysis of the effect of diet on the concentration of urea in the blood at any given ratio in percentage of mean normal is shown in chart 8. The curves presented were drawn according to formulas derived from the exponential equations for adjusted curves for urea in the blood and the urine in chart 7. No significant difference in the concentration of urea in the blood is noted until the urea ratio reaches a level of about 15. As renal insufficiency becomes more severe, the differences in the concentration are greater between the various dietary groups. The curves for the animals fed the EM 40, the EM 60 and the EM 80 diet do not reach the zero urea ratio line at a level of 800 mg of urea per hundred cubic centimeters of blood, which is in striking contrast to similar curves obtained for animals ingesting diets containing dried whole meat.

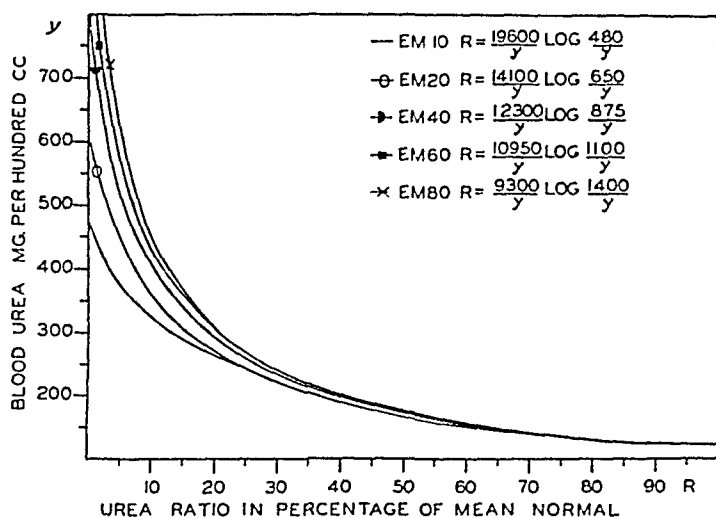


Chart 8—Relation between the concentration of urea in the blood and the urea ratio in percentage of the mean normal value

SUMMARY

The effect of feeding diets containing various percentages (10, 20, 40, 60 and 80) of dried extracted meat to intact, unilaterally and partially nephrectomized rats has been studied.

Data showing the effects of these diets on renal hypertrophy, renal function and blood pressure of intact and unilaterally nephrectomized rats are presented. The blood pressure and $\frac{\text{heart weight}}{\text{surface area}}$ remained constant, the $\frac{\text{kidney weight}}{\text{surface area}}$ ratio increased progressively and the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio was fairly constant for the intact rats.

The following observations were made on the partially nephrectomized rats

The incidence of hypertension was high for all groups except those fed the diet containing 80 per cent dried extracted meat. The correlation between $\frac{\text{heart weight}}{\text{surface area}}$ ratios and blood pressure was low for groups ingesting 60 and 80 per cent extracted meat.

The total solids of the kidneys per unit of surface area increased progressively with increased ingestion of protein.

The urinary volumes during a concentration test were smallest for the rats fed the EM 10 diet and greatest for those fed the EM 40 diet. The greatest incidence of low specific gravities was obtained for groups on the diets containing the higher amounts of protein (40, 60 and 80 per cent). Proteinuria was most marked in those fed the EM 40 diet. According to the results of the concentration test, the most marked changes in renal function were noted in rats on the EM 40 diet.

Renal insufficiency, as judged by the urea clearance test, was most marked in the group fed the EM 40 diet and least marked in the group fed the EM 80 diet. Curves showing the relation of diet to the urea in the blood and the urine demonstrate that extremely high concentrations of urea in the blood are associated with low urea ratios.

INTRACEREBRAL CARCINOMATOUS METASTASES

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There are apparently several ways by which carcinoma may metastasize to the central nervous system. Briefly, these are (1) by direct extension (along nerve sheaths, by bony invasion or from the meninges), (2) through the lymphatic vessels, usually in retrograde growth, and (3) via the blood stream, as carcinomatous emboli. The different routes of invasion result in different pathologic¹ and clinical pictures.

Direct extension may be from a nearby primary focus, as in the case of carcinoma of the nasopharynx, or from a distant focus preceded by metastasis to a nearby structure, as in the case of carcinoma metastatic to the skull from the thyroid or the prostate. The resultant clinical picture is a combination of the symptoms produced by the structures primarily involved and those produced by the later growth into the central nervous system. Metastasis by the lymphatic route results usually in so-called meningitis carcinomatosa, with the well known picture of diffuse meningeal and encephalic disturbance. This syndrome has been described by a number of writers, including Schwarz and Bertels,² Panchotoni,³ Boyd,⁴ Lewis,⁵ Fried⁶ and Cornwall.⁷ The

Read in part at a meeting of the Neurological Society of Rhode Island, Providence, R I, April 12, 1937

1 Winkelman, N W, and Eckel, J L. Metastatic Carcinoma of the Central Nervous System, *J Nerv & Ment Dis* **66** 1-14 (July), 133-148 (Aug) 1927

2 Schwarz, E, and Bertels, A. Ueber "Meningitis" carcinomatosa, *Deutsche Ztschr f Nervenhe* **42** 85-94, 1911

3 Panchotoni, D. Ueber diffuse Karzinomatose der weichen Hirnhäute, *Arch f Psychiat* **49** 396-405, 1912

4 Boyd, W. Diffuse Tumors of the Meninges, *Am J Path* **1** 583-593 (Nov) 1925

5 Lewis, N D C. An Unusual Manifestation of Metastatic Miliary Carcinomatosis of the Central Nervous System, *Am J Psychiat* **5** 171-187 (Oct) 1925

6 Fried, B M. Sarcomatosis of the Brain, *Arch Neurol & Psychiat* **15** 205-217 (Feb) 1926

7 Cornwall, L H. Metastatic Meningo-Encephalic Carcinomatosis Without Tumefaction, *Arch Neurol & Psychiat* **17** 466-470 (April) 1927

brain may be invaded directly from this diffuse focus, but the symptoms are overshadowed by the diffuse meningeal and encephalic involvement. The blood stream seems to be the most frequent route of carcinomatous metastasis to the central nervous system. In this type of metastasis the lesions develop within the neural parenchyma. Depending on the number and location of the metastatic nodules the clinical picture may be that of a tumor of the brain or that of a diffuse cerebral disease. It is the latter type of metastatic cerebral disease with which we are concerned in this communication.

The clinical diagnosis of cerebral metastasis is usually easily established when the patient is known to have a primary carcinomatous tumor. When the history, symptoms or signs of primary carcinoma are lacking the diagnosis may be difficult to make and may be established only after a craniotomic operation. A search for the primary tumor then leads to its discovery, and its location is most commonly in the lungs. In some cases the diagnosis is established at the autopsy table.⁸ Common incorrect clinical diagnoses are primary tumor of the brain, cerebral hemorrhage or thrombosis, encephalitis, abscess of the brain and, in the earlier stages of the illness, psychoneurosis or psychosis.

Our purpose in this paper is to describe the clinical features of 100 cases of intracerebral carcinomatous metastases studied at the Neurological Institute of New York and the Presbyterian Hospital and the pathologic features in 34 of these cases in which autopsy was performed, as studied in the departments of neuropathology of these two hospitals. We have also attempted to compare the features in our group of cases with some of those recorded in the literature. We have limited our study to cases in which the tumor has spread, presumably by way of the blood stream, to involve the parenchyma of the brain and have omitted those in which metastasis has occurred by direct extension or by the lymphatic vessels to involve the bones of the skull or the meninges primarily.

FREQUENCY

There are numerous reports of cerebral metastatic carcinomatous tumors in the literature, and since these reports come from varied sources one may conclude that the disease occurs rather commonly. Statistics from a hospital specializing in the treatment of neurologic

⁸ Ferguson, F. R., and Rees, W. E. Cerebro-Spinal Metastases from Unsuspected Pulmonary Carcinoma, *Lancet* **1** 738-744 (April 5) 1930. Dickson, W. E. C., and Worster-Drought, C. Multiple Metastatic Tumours in the Brain Arising from Primary Bronchial Carcinoma, *J. Neurol. & Psychopath.* **16** 289-320 (April) 1936.

diseases are not a true index of the frequency of metastatic tumors but provide an index of their frequency in comparison with that of other tumors of the brain. Operative statistics alone are of little value in such a study. Cushing,⁹ in the report of 2,000 cases of tumor of the brain in which the diagnosis was neurosurgically verified, stated that 65, or 3.2 per cent, of the tumors were metastatic but explained that this relatively low incidence was due to the surgeon's reluctance to operate on metastatic growths. In his series, 48 of the 65 metastatic tumors were carcinomatous. Elkington,¹⁰ in his studies of the records of the National Hospital, Queen Square, London, England, found that in sixteen years (1918-1933) there were 805 cases of tumor of the brain in which the diagnosis was histologically verified, and 72, or 9 per cent, of the growths were metastatic. Garland and Armitage,¹¹ in 264 autopsies on patients who died of cerebral tumor in the Leeds General Infirmary, Leeds, England, found that 12.8 per cent of the tumors were metastatic. Elkington¹⁰ stated that it is reasonable to assume that not less than 20 per cent of all tumors of the brain are metastatic. Roger and Paillas¹² found that metastatic tumors constitute 10 per cent of all cerebral tumors seen at the Neurological Clinic at Marseilles, France. Shelden,¹³ in a report of cases from the Mayo Clinic, estimated that 5 per cent of all tumors of the brain studied there are metastatic. He concluded, however, that the percentage may well be higher than this. Bailey¹⁴ estimated from his study of intracranial tumors that metastatic tumors constitute 33 per cent of all tumors of the brain and from the neurosurgical statistics, that they form about 4 per cent. He concluded that both estimates are wrong, for they probably comprise less than 33 per cent of all tumors and more than 4 per cent as verified after craniotomy. We feel that

9 Cushing, H. *Intracranial Tumours. Notes upon a Series of Two Thousand Verified Cases with Surgical-Mortality Percentages Pertaining Thereto*, Springfield, Ill., Charles C Thomas, Publisher, 1932.

10 Elkington, J. St. C. *Metastatic Tumours of the Brain*, *Proc Roy Soc Med* **28** 1080-1096 (June) 1935.

11 Garland, H. G., and Armitage, G. *Intracranial Tuberculoma*, *J Path & Bact* **37** 461-471 (Nov.) 1933.

12 Roger, H., and Paillas, J. E. *Les tumeurs cerebrales metastatiques. Etude clinique*, *Presse med* **42** 2093-2096 (Dec 29) 1934.

13 Shelden, W. D. *Secondary Tumors of the Brain*, *J A M A* **87** 650-654 (Aug 28) 1926.

14 Bailey, P. *Intracranial Tumors*, Springfield, Ill., Charles C Thomas, Publisher, 1933, chap 17, pp 348-368.

statistics from the Neurological Institute would add little but confusion to the varying data, but we believe that the actual incidence of metastatic cerebral tumors is somewhere between 10 and 20 per cent of all tumors of the brain

CEREBRAL METASTASIS IN RELATION TO MALIGNANT DISEASE

Statistics, to be of any value in determining the relation of cerebral metastases to primary carcinoma elsewhere in the body, must come from large series of autopsies. Rau¹⁵ observed cerebral metastases in 3.2 per cent of 851 cases of carcinoma, and Krasting¹⁶ in 4.7 per cent of 817 cases. Krasting stated that intracranial metastases follow 18 per cent of all primary carcinomas, this percentage being based on his own statistics and those of Starr, Guilt and Gallavardin and Varay.

In a study of the statistics on primary bronchogenic carcinoma a much higher percentage of metastases is found. Thus, Fried and Buckley,¹⁷ in a study of 38 cases of proved primary bronchogenic carcinoma, observed pathologically verified metastases in the brain in 15 cases (39.2 per cent). Dosquet¹⁸ of 105 cases of bronchial carcinoma observed cerebral metastases in 31 per cent. Seyfarth,¹⁹ on the other hand observed metastasis to the brain in only 9.7 per cent of 309 cases. Davison and Horwitz²⁰ found 11 per cent in which primary carcinoma in the lungs involved the central nervous system. In 6 cases in which autopsy was done there was cerebral involvement. We feel that our cases could add little, if anything, to these facts.

15 Rau, W. Eine vergleichende Statistik der in 5 Kriegsjahren (1914-1919) und 5 Friedensjahren (1909-1914) seziierten Fälle von Krebs und anderen malignen Tumoren am pathologischen Institut des Stadtkrankenhauses Dresden-Friedrichstadt, *Ztschr f Krebsforsch* **18** 141-170, 1921.

16 Krasting, K. Beitrag zur Statistik und Kasuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentralnervensystem (auf Grund von 12730 Sektionen der pathologisch-anatomischen Anstalt Basel), *Ztschr f Krebsforsch* **4** 315-379, 1906.

17 Fried, B. M., and Buckley, R. C. Primary Carcinoma of the Lungs. IV. Intracranial Metastases, *Arch Path* **9** 483-527 (Feb.) 1930.

18 Dosquet, H. Ueber die Metastasenbildung bei primären Lungen- und Bronchialkrebsen, *Virchows Arch f path Anat* **234** 481-484, 1921.

19 Seyfarth, C. Lungenkarzinome in Leipzig, *Deutsche med Wchnschr* **50** 1497-1499 (Oct.) 1924.

20 Davison, C., and Horwitz, W. A. Primary Carcinoma of the Lungs with Metastases to the Central Nervous System, *Arch Int Med* **46** 680-704 (Oct.) 1930.

SITE OF PRIMARY GROWTH

The sites of the primary growth in our group of 100 cases are shown in the following tabulation

Site	No. of Cases, or Percentage
Bronchus	42
Breast	23
Stomach	3
Intestine	3
Colon	1
Rectum	1
Ovaries	1
Uterus	1
Kidneys	2
Penis	1
Adrenal glands	2
Thyroid	2
Scalp	1
Skin of finger	1
Undetermined	16
Total	100

It is evident that the great majority (65 per cent) of cerebral metastases have their origin either in the lung or in the breast. This percentage may well be greater than that indicated, as the primary site was undetermined in 16 per cent of the cases.

The pulmonary origin of the primary growth in 42 per cent of our cases is in agreement with the data of Meagher and Eisenhardt,²¹ who found that 35 per cent of metastases in their cases originated in the lung. In the 72 cases reported from the National Hospital¹⁹ 33.3 per cent of the metastases originated in the bronchus, whereas Grant,²² in 43 cases, found a bronchial origin in only 13.5 per cent. Other reports show variation in the percentage frequency of the bronchus as a primary site, but most of them place it between 30 and 50 per cent.

In our series of 100 cases 23 per cent of metastases originated in the breast. This conforms with the statistics of others: e. g., Meagher and Eisenhardt, 25 per cent, Elkington, 18 per cent, and Grant, 31.3 per cent.

Other sources of the primary growth appear in the published reports in about the same percentage relation as is shown in table 1.

21 Meagher, R., and Eisenhardt, L. Intracranial Carcinomatous Metastases* with Note on Relation of Carcinoma and Tubercle, *Ann Surg* **93** 132-140 (Jan.) 1931.

22 Grant, F. C. Concerning Intracranial Malignant Metastases: Their Frequency and the Value of Surgery in Their Treatment, *Ann Surg* **84** 635-646 (Nov.) 1926.

In our series the left breast was primarily involved in 12 and the right breast in 11 cases. The left bronchus was the primary site in 14 and the right in 18, of the cases in which a definite laterality could be determined.

INCIDENCE

Age—The incidence according to age in our series of 100 cases is shown in the following tabulation:

Age, Years	No. of Cases
10-20	1
20-30	4
30-40	22
40-50	34
50-60	29
60-70	9
70-80	1
Average age, 44.6	

The youngest patient in the group was a girl 12 years of age, with a primary carcinoma of the thyroid. The oldest patient was 70, with metastasis presumably from the gastrointestinal tract. The average age of 44.6 years compares with Elkington's average of 47 years.

It is of interest to note that in our series 27, or 27 per cent, of the patients were less than 40 years of age.

Sex—There were 54 males and 46 females in the series. In the group of patients with the primary tumor in the lung it is of interest to note that there were 32 males, as compared with 10 females.

DURATION OF SYMPTOMS

The duration of neurologic symptoms prior to entrance to the hospital varied from a few days to one and a half years. In 84 of the 100 cases symptoms were present for less than five months. In 6 cases symptoms were present for one year or more. In 2 instances neurologic symptoms were lacking. The following tabulation shows the duration of symptoms before the patients were admitted to the hospital.

Duration	No. of Cases
1-5 weeks	30
5-10 weeks	30
10-20 weeks	24
20-30 weeks	5
30-40 weeks	3
12 months	4
14 months	1
18 months	1
No symptoms	2

Cerebral symptoms of a primary tumor of the brain are usually of much longer duration prior to hospitalization than were the symptoms in this group of metastatic tumors. Glioblastoma multiforme is, however, an exception²³

Of the 6 cases in which symptoms were present for one year or more, it was observed that there were metastases from the lung in 3, from the breast in 1, from the gastrointestinal tract in 1 and from an undetermined source in 1

DURATION OF LIFE

The duration of life in this group is measured as from the occurrence of the first neurologic symptom to the time of death. In some cases this has not been determined, because we were unable to ascertain whether or when death occurred. In the group of 34 cases in which autopsy was performed in our own laboratories the time varied between three weeks and fifteen months and averaged three and six-tenths months. In an additional group of 40 patients discharged from the hospital, who later died, we found the average duration of life to be six and four-tenths months. In this group death followed the initial cerebral symptom in periods ranging from two weeks to twenty-five months. The case of the 1 patient who survived for twenty-five months after signs of cerebral metastasis from a primary tumor of the breast is unusual. Of the remainder of the group, 7 survived for approximately fifteen months.

In Elkington's series the average duration of life after the onset of cerebral symptoms was six and three-tenths months, which is, strangely, in close accordance with the average of six and four-tenths months for our patients who died after leaving the hospital.

MODE OF ONSET

The initial symptom referable to intracranial disease appeared in one of three general manners, these are classified as sudden, rapid or gradual. The onset in 5 cases did not fit into this classification. In 2 of these there were no neurologic symptoms, and in the 3 others we were unable to classify the mode of onset because of confusing statements in the case history.

²³ Globus, J. H., and Selinsky, H. Metastatic Tumors of the Brain. A Clinical Study of Twelve Cases with Necropsy, *Arch Neurol & Psychiat* **17** 481-513 (April) 1927.

In 36 of the 100 cases the onset of symptoms was sudden. The first symptoms were as follows:

Symptom	No. of Cases
Convulsive seizures	10
General	7
Jacksonian	3
Headache, vertigo and vomiting	8
Headache	5
Hemiplegia or hemiparesis	3
Aphasia	2
Vertigo	2
Mental disorder	1
Headache and diplopia	1
Headache and hemiplegia	1
Headache and dysarthria	1
Scotomas	1

The intracranial symptoms developed rapidly in 42 cases. In this group the first symptoms were:

Symptom	No. of Cases
Headache	30
Mental disturbances	5
Hemiparesis	2
Monoparesis	1
Sensory disturbances	1
Diplopia	1
Diplopia and tinnitus	1
Vomiting	1

A gradual onset was recorded in 17 cases. The symptoms were at first mild and were slower in their progressive development than in the other two groups. The first symptoms were:

Symptom	No. of Cases
Headache	10
Mental disturbances	3
Failing vision	2
Hemiparesis	1
Monoparesis	1

Thus, the manner of onset of intracranial symptoms in at least 78 cases appears to be different from that observed in cases of other tumors of the brain, except glioblastoma multiforme. In the cases of sudden onset there were manifestations similar to those associated with cerebral vascular accidents. The mode of onset in these cases certainly simulates that seen in patients in whom a non-neoplastic embolus suddenly lodges in a cerebral vessel.

SYMPTOMS

General Symptoms—Forty of the 100 patients appeared to be in good general health. In this group the signs so often suggestive of malignant tumor were lacking. There were indications of some weakness and increasing fatigability, associated with a slight loss of weight, in 31 of the remaining patients. In 29 there were pronounced cachexia and signs of a debilitating disease. Fever was an outstanding symptom in only 2 cases.

Headache—Headache of varying degrees was an outstanding symptom in 83 of the 100 cases. In 49 instances it was associated with various degrees of papilledema. In 34 there was headache without associated papilledema. Seventeen patients did not complain of headache, and none of these had papilledema.

The headache was frequently well localized and commonly paroxysmal. In many cases it was severe and was associated with vomiting. In most cases it was not relieved by the usual dehydration methods or by the use of drugs of such strength as one hesitates to prescribe for the usual headache due to tumor of the brain. The headache, for which little relief was offered, was one of the most distressing features of the disease to both patient and physician.

Vomiting—Vomiting occurred during some stage of the illness of 59 patients. It was frequently associated with periodic headache or vertigo and was often projectile.

Mental Alterations—There were mental alterations of varying degrees in 50 of the 100 cases. In this group there were true mental alterations during the earlier part of the illness. The change was of mild degree in 29 and was characterized by slowness in mental reaction, faulty memory, mild degrees of depression, emotional instability, irritability, loss of interest and reduced powers of attention.

Pronounced alterations in mentality were observed in 21 patients. In these, in addition to greater degrees of the symptoms aforementioned, there was usually profound mental confusion. Patients of this type required constant nursing. They were incontinent, required spoon feeding and often had to be restrained in bed. Hallucinations were not infrequent. At times the confusional states cleared so that the patients were perfectly rational, with good insight. It seems plausible that the mental symptoms, at least in some instances, were intensified by general systemic toxemia, such as one sees in patients with carcinoma without metastases to the brain. The incidence (50 per cent) of mental symptoms appears to be higher than in patients with nonmetastatic tumors.

In the remaining group of 50 patients, considered to be without mental disturbances, there were some who were somnolent or stuporous for four to seven days before death.

Convulsive Seizures—Twenty of the 100 patients had one or more convulsive seizures. Focal motor seizures without loss of consciousness

were present in 9 cases and focal sensory seizures in 2. Generalized convulsive seizures with loss of consciousness occurred in 7 patients. One had both general and focal seizures. In 1 patient there was periodic loss of consciousness, with an aura consisting of auditory, uncinate and gustatory phenomena and without any actual motor activity.

Autopsies were performed on 6 of these patients. Autopsy revealed a single metastatic nodule in the motor arm area of the left precentral gyrus of a patient who had previously had clonic movements of the right arm. Periodic sensory disturbances on the left side had been observed in 1 patient, and these were later replaced by motor convulsions. At autopsy one metastatic tumor nodule was seen in the right postcentral and precentral islandic convolutions. Two patients had generalized convulsive seizures, and multiple nodules were observed in the brain at autopsy. Two other patients had unilateral seizures, and multiple nodules were seen at autopsy.

The convulsive phenomena outlined appeared to correspond with lesions in the cerebral areas, which was to be expected. In 2 cases they localized single metastatic nodules, in 4 others they localized only one of many nodules.

SIGNS REFERABLE TO CEREBRAL DESTRUCTION OR DIRECT COMPRESSION

There was clinical evidence of either destruction or direct compression of brain tissue in 68 of the 100 cases. The motor components were most commonly involved. The following disorders were observed in 68 patients, several of whom had more than one of the signs enumerated.

Symptom	No. of Patients
Hemiplegia	22
Monoplegia	5
Paraplegia	1
Quadriplegia	1
Slight hemiparesis	5
Slight monoparesis	1
Local sensory disturbances	8
Ataxia	16
Aphasia	21
Apraxia	1
Deafness	2
Dysphagia	1
Dysphonia	1
Dysarthria	1
Trigeminal pain	2
Trigeminal anesthesia	3
Facial paralysis (peripheral)	2
Hemianopia	5
Urinary disturbances	2

The signs outlined were usually of marked degree and showed no evidence of improvement, they were more apt to become progressively worse. The exception to this was the peripheral facial paralysis, which cleared up in about ten days. Patients with hemiplegia often had monoplegia first. The ataxia was frequently truncal. Aphasia and hemiplegia occurred commonly in combination in the same patient. Hemianopia, when present, was usually homonymous.

VISUAL SYMPTOMS REFERABLE TO INCREASED INTRACRANIAL PRESSURE

Thirty-five patients showed visual symptoms referable to increased intracranial pressure, although many, such as blurring of vision, were mild. Diplopia, usually transient, was a prominent symptom in 10 cases and was apparently due to general pressure on either one or both of the abducens nerves intracranially, so that paresis of the lateral rectus muscle resulted. Seventeen of the group complained of blurred vision, which appeared to be caused by papilledema. Two patients complained of photophobia. Amblyopia was present in 1 patient despite absence of papilledema or atrophy of the optic nerve. A single cerebellar metastasis, observed at autopsy, did not appear to explain this condition.

MENINGEAL IRRITATION

Some writers have recorded meningeal irritation as a common symptom. We observed it in 7 patients. It was evidenced by slight nuchal rigidity and a subjective sense of stiffness of the cervical muscles, associated with severe headache.

PAPILLEDEMA

Well defined papilledema of measurable degree often accompanied by retinal hemorrhages, was seen in 31 of the 100 patients. In 40 additional patients the heads of the optic nerves were hazy or blurred. The opinions of different observers varied as to whether this represented beginning papilledema. The optic fundi appeared normal in the remaining 29 cases. Secondary atrophy of the optic nerve did not develop because of the relatively short duration of the papilledema prior to death.

SYMPTOMS REFERABLE TO THE PRIMARY GROWTH

The 23 patients with tumors of the breast all had shown definite indications of the condition, and in all instances a mastectomy had been performed. There were definite signs of a primary malignant tumor in 18 additional patients, and in the cases of many of these previous histologic studies had established the diagnosis. Symptoms suggestive

of a primary malignant tumor were present in 9 cases. These included slight cough, pain in the chest, hemoptysis and gastrointestinal disturbances. In 34 cases symptoms referable to a primary malignant tumor were lacking or were not elicited. Cases of carcinoma of the lung formed the greater part of the last group, and, as has been emphasized by Bunts,²⁴ the intracranial disease was the earliest evidence of the pulmonary condition. In 16 cases (table 1) the original site of the malignant growth was not determined.

Only 2 of the 42 primary bronchial growths produced signs which pointed definitely to the source. These signs were fever, chills, cough and hemoptysis. In 10 additional cases there were suggestive symptoms such as slight cough with or without hemoptysis, and in a few there was pain in the chest. Thirty of the primary bronchial growths failed to produce symptoms. Elkington¹⁰ observed symptoms referable to the chest in 7 of his 9 cases of bronchogenic carcinoma. These symptoms were not severe enough for the patients to consult a physician, but were elicited on questioning after the onset of cerebral symptoms.

CEREBROSPINAL FLUID

A study of the cerebrospinal fluid was made in 54 of the 100 cases and of the ventricular fluid in 5 additional ones. In 38 (70.3 per cent) of the 54 cases the spinal fluid was abnormal, with regard chiefly to an increase in the total protein content and the globulin reaction and in a few specimens to an increase in the cellular content. A positive Wassermann reaction was obtained in the stronger dilutions in 3 specimens. Only 1 such reaction was associated with a positive Wassermann reaction of the blood. Three of the 5 specimens of ventricular fluid were abnormal in the same respect as the spinal fluid.

The spinal manometric pressure was recorded in 18 instances, and in these it was greater than the top normal value of 180 mm of water in 7 cases. Slight leukocytosis was found in 7 of the 54 specimens, and for these the cell counts were recorded as 55, 50, 48, 17, 15, 12 and 11 per cubic millimeter, respectively. Lymphocytes predominated in all. This cellular increase in the spinal fluid occurs with about the same frequency as in cases of primary cerebral neoplasm, according to a previous study by one of us (C. C. H.)²⁵ of 186 such cases.

The total protein content was increased in 38 specimens and measured between 56 and 241 mg per hundred cubic centimeters. The

24 Bunts, A. T. Intracranial Metastasis as Earliest Evidence of Carcinoma of the Lung, *Cleveland Clin Quart* 3:234-241 (July) 1936.

25 Hare, C. C. The Cerebrospinal Fluid Obtained by Lumbar and by Ventricular Puncture in Tumors of the Brain, *Bull Neurol Inst New York* 4:64-90 (March) 1935.

globulin reaction in a like number of specimens was increased to from 1 to 3 plus

ROENTGEN STUDY OF THE SKULL

Stereoscopic roentgenograms of the skull were taken in 91 of the 100 cases. They appeared normal in all respects in 40 and abnormal in 51. Metastases to the bones of the skull were seen in 15 cases. A calcified pineal gland was displaced in 24 additional cases. Erosion of the clinoid processes or the dorsum of the sella turcica was evidence of increased intracranial pressure in 22 cases. In many of the last-mentioned group the pineal gland was also displaced. Calcification in a tumor mass was observed in the roentgenogram of the skull in 1 case.

Encephalographic studies were made in 10 cases, and in 8 of these there were abnormalities indicative of a tumor. Ventriculograms were taken in 9 additional cases. Six were abnormal but lacked evidence for a positive diagnosis of tumor or for localization of the growth. In the remaining 3 there was definite localization of a tumor.

The erosion of portions of the sella turcica in 25 cases is of interest. In 10 of these the period elapsing between the first neurologic symptom and the roentgenographic study of the skull was less than three months. The changes in the sella turcica in these 10 cases were slight, but were considered definitely abnormal.

The calcification observed in the tumor in 1 case is of interest, for usually the metastatic mass is present for too short a time to permit such a change. In this particular case a mammary carcinoma had been removed five years previously, and cerebral symptoms were noted only two months prior to roentgen study of the skull. At autopsy three tumor masses were observed in the brain, one corresponding in location with the calcification seen on the roentgenograms. All three masses contained areas of caseous degenerated tissue.

ROENTGEN STUDY OF THE CHEST

Roentgenograms of the chest were taken in 35 of the 42 cases in which a bronchogenic carcinoma was diagnosed at autopsy. A roentgen diagnosis of primary tumor of the lung was made in 27 of the 35 cases. In 7 other cases the roentgenologist reported changes in the lungs suggestive of an infectious process, including enlargement of the peribronchial lymph nodes in 1 instance and pleural effusion in another. In only 1 case were the roentgenograms entirely normal. Not infrequently the primary bronchogenic carcinoma is so small that even at autopsy it is seen only after prolonged search. It may originate in a secondary or tertiary bronchial tube.

Roentgenograms of the chest were taken in 20 of the 23 cases of primary carcinoma of the breast. Metastases to the lung were seen in

14 of the 20 cases. A shadow suggestive of an aneurysm appeared in the roentgenograms of 1 patient. Permission for autopsy was not obtained in this case. In 2 cases the lungs appeared entirely free of metastases.

Roentgenograms of the chest were taken in 5 of the 8 cases of tumor primary in the gastrointestinal tract; in only 1 were there signs of metastasis, and that was from the colon.

Roentgenograms of the chest in the cases of primary growths in the ovaries or adrenal glands showed nothing abnormal. Pulmonary metastases were present in each of the cases of primary carcinoma of the penis or uterus. One of the 2 renal tumors metastasized to the lung as did 1 of the 2 carcinomas of the thyroid.

Of the 16 cases in which the site of the primary growth was undetermined, roentgenograms of the chest were taken in 8; they were normal or showed an old infectious process. In 1 a tumor of the lung was suspected.

DIAGNOSIS

The diagnosis is simple in cases in which there are a known primary carcinoma of the breast and later signs indicative of a cerebral neoplasm. The metastases may occur a number of years after surgical or roentgen treatment of the mammary tumor. In 22 of our 23 cases of metastatic carcinoma of the breast, the interval between the mastectomy and the first neurologic symptom averaged twenty-five months. The shortest interval was four months and the longest six years, except in 1 instance, in which the neurologic signs preceded the mastectomy. The metastases occurred despite the fact that most of the mastectomies were of the radical type and were followed by roentgen therapy. Unfortunately no complete data are available regarding the duration and amount of the roentgen therapy and the extent of the operative procedures. Frequently the metastases pass first to the lungs and may be seen there in roentgenograms. In all the cases in our series the correct diagnosis was made.

When the primary growth is in the bronchial tissue and there are signs of a tumor of the brain an incorrect diagnosis is common. This results either from failure to elicit a history of any bronchial disturbance or from failure of symptoms of such a disturbance to develop. Roentgen studies of the chest are therefore often omitted and clinical examination of the chest rarely aids in diagnosis of a small growth. It is therefore not known that a bronchogenic carcinoma is present and all efforts are aimed at determining the cause of the presenting cerebral disturbances. This is then often determined to be a primary tumor of the brain, usually of glomatous origin. It may be only after the surgeon has performed a craniotomy and has examined a specimen of the tumor tissue histologically that the true nature of the disease is known.

Roentgenograms of the chest then usually reveal a tumor arising from a bronchus. In other cases in which the surgeon fails to find the tumor tissue in the brain the diagnosis may be made only at the autopsy table. Probably in many instances the correct diagnosis is never established.

In many cases of undetermined bronchogenic carcinoma the cerebral disturbances may be diagnosed as resulting from cerebral thrombosis or hemorrhage, abscess of the brain, subdural hematoma, cerebral aneurysm, encephalitis or cerebral arteriosclerosis. In our series of cases such a diagnosis was commonly made by one or more of the many physicians who examined each patient clinically.

In cases in which there is a primary growth elsewhere than in the bronchial tree there are usually indications which lead to the diagnosis of carcinoma before cerebral metastases occur.

PATHOLOGIC STUDIES

Autopsy studies were made in our own pathologic laboratories in 34 of the 100 cases. In most cases a complete autopsy was permitted, in others the contents of the cranial cavity only were examined. In 6 additional cases autopsy reports confirming the presence of cerebral carcinomatous metastases were received from laboratories of other hospitals. Data from these reports are not included in the following sections.

Gross Appearance of the Brain—The outstanding feature was the asymmetry of the cerebral or cerebellar hemispheres with distortion of the associated structures. These changes were not extensive but were localized to the regions invaded by the carcinoma. In most cases the ventricular systems were involved in the distortion. The cerebral gyri were frequently flattened and the sulci narrowed, and the entire brain had a swollen, edematous appearance. Tumor masses extended to the cortical surface in only 2 brains. A distinct herniation of the cerebellar structures into the foramen magnum was seen in 3 cases.

Number of Tumors—Multiple tumors were present in 20 brains and single tumors in 14.

Position of Tumors—The cerebrum was involved in 26, the cerebellum in 16, the brain stem in 6 and the pituitary gland in 2 cases. Single nodules were observed in one cerebellar hemisphere in 5 cases and in one cerebral hemisphere in 8 cases. A single metastatic nodule was seen within the medulla oblongata in 1 case.

Elkington¹⁰ pointed out that these types of tumor invariably involve the brain substance at the junction of the central white and the cortical gray matter. This localization of the metastatic nodules within the parenchyma was observed in the great majority of our cases (fig 1). Most of the larger tumors seemed to extend into the white rather than the

gray matter. Ellington¹⁰ further pointed out that the junction between white and gray matter is the usual location of metastatic abscesses of the brain. He suggested that the predilection of this area for blood-borne foreign bodies may be due to the breaking up of the pial arterioles into their terminal capillaries at this point.

Appearance of Tumors—The tumor masses varied greatly in size. As a rule, if large tumors were present they were few. The larger

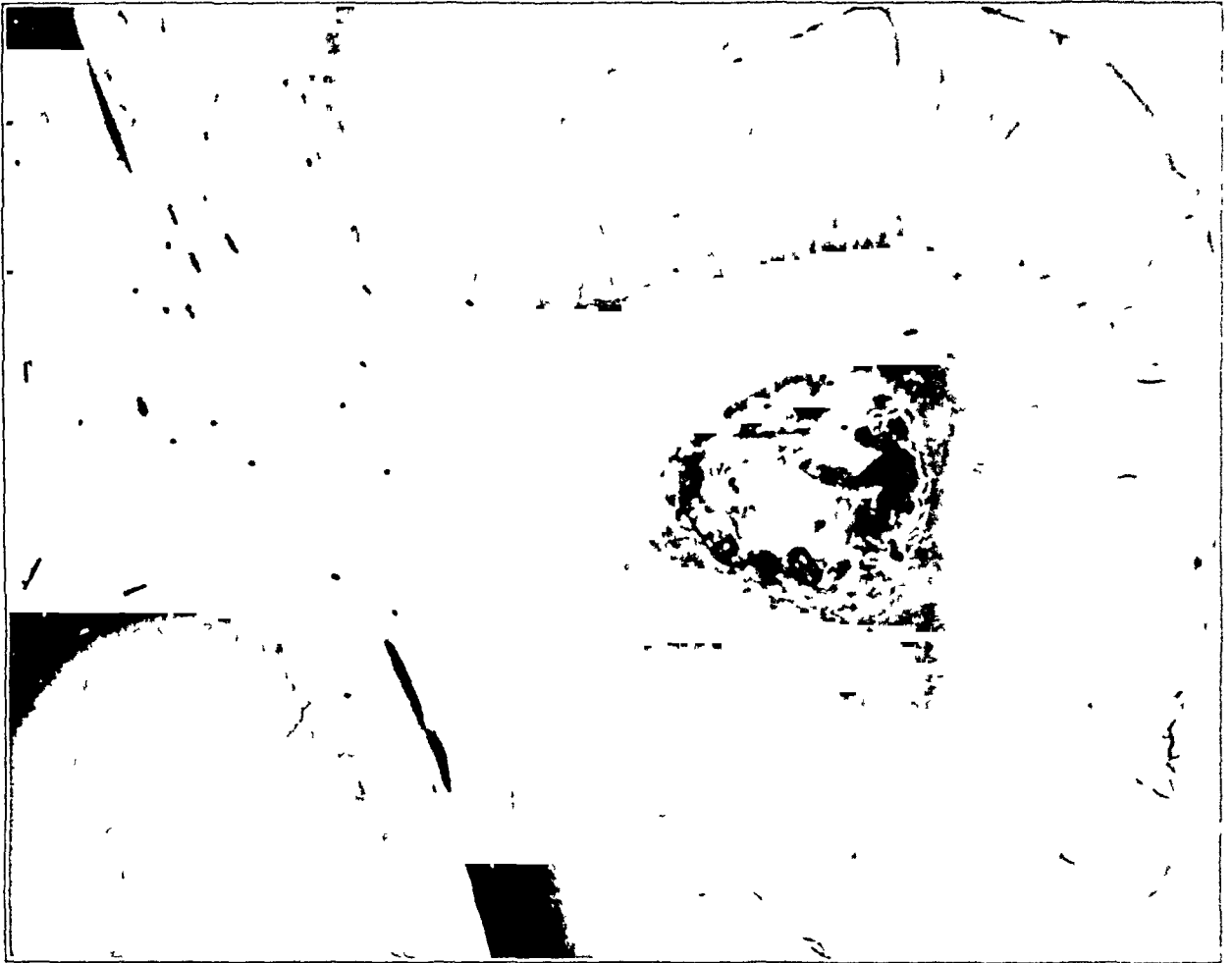


Fig. 1—Military nodule of a carcinoma metastatic to the cerebrum. Note the position of the nodule at the junction of the gray and the white matter. The photomicrograph shows well the destruction of the parenchyma at the site of the lesion. Note the good preservation of the myelin in the vicinity of the metastatic tumor. Pal-Weigert stain, $\times 12$.

masses frequently measured 5 to 10 cm. in diameter. In some brains great numbers of pinhead-sized tumors were present, the brain giving the appearance of having been sprayed with metastases.

The larger tumors were commonly composed of soft degenerated tissue and in some instances were actually cystic. The firmer tumors

were well demarcated, and some shelled out easily from the formaldehyde-hardened brain tissue

Appearance of Meninges—The dura was grossly involved by a large tumor in 2 cases. In 1 of these the frontal bone was also eroded. The

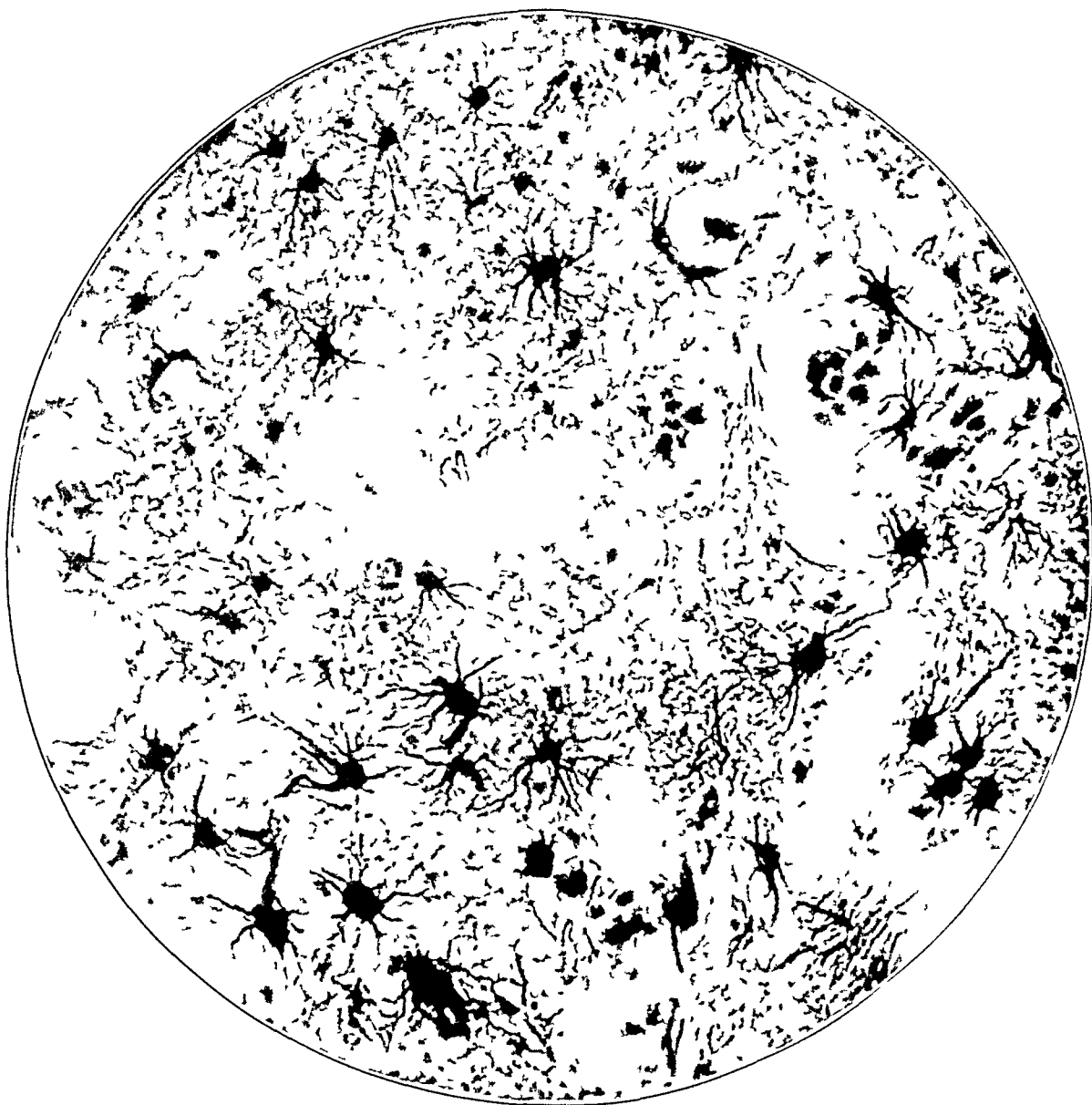


Fig 2—Reactive astrocytosis at the margins of the metastatic carcinoma nodule in the brain. Cajal stain, $\times 454$

pia-arachnoid was grossly involved in the vicinity of the underlying tumor in 2 additional cases. No cases of meningeal carcinomatosis were included in our series.

Metastases to Structures Other Than the Brain—In only 2 of the 20 cases of primary carcinoma of the lung was the brain the sole recipient of metastases. The other structures most commonly involved

were (1) the regional lymph glands, (2) the adrenal glands, (3) other pulmonary areas and (4) the liver. Less commonly affected structures were the ovaries, pancreas, pericardium, diaphragm, long bones, kidneys, spleen and periprostatic tissue. In 3 of the 9 cases of primary tumor

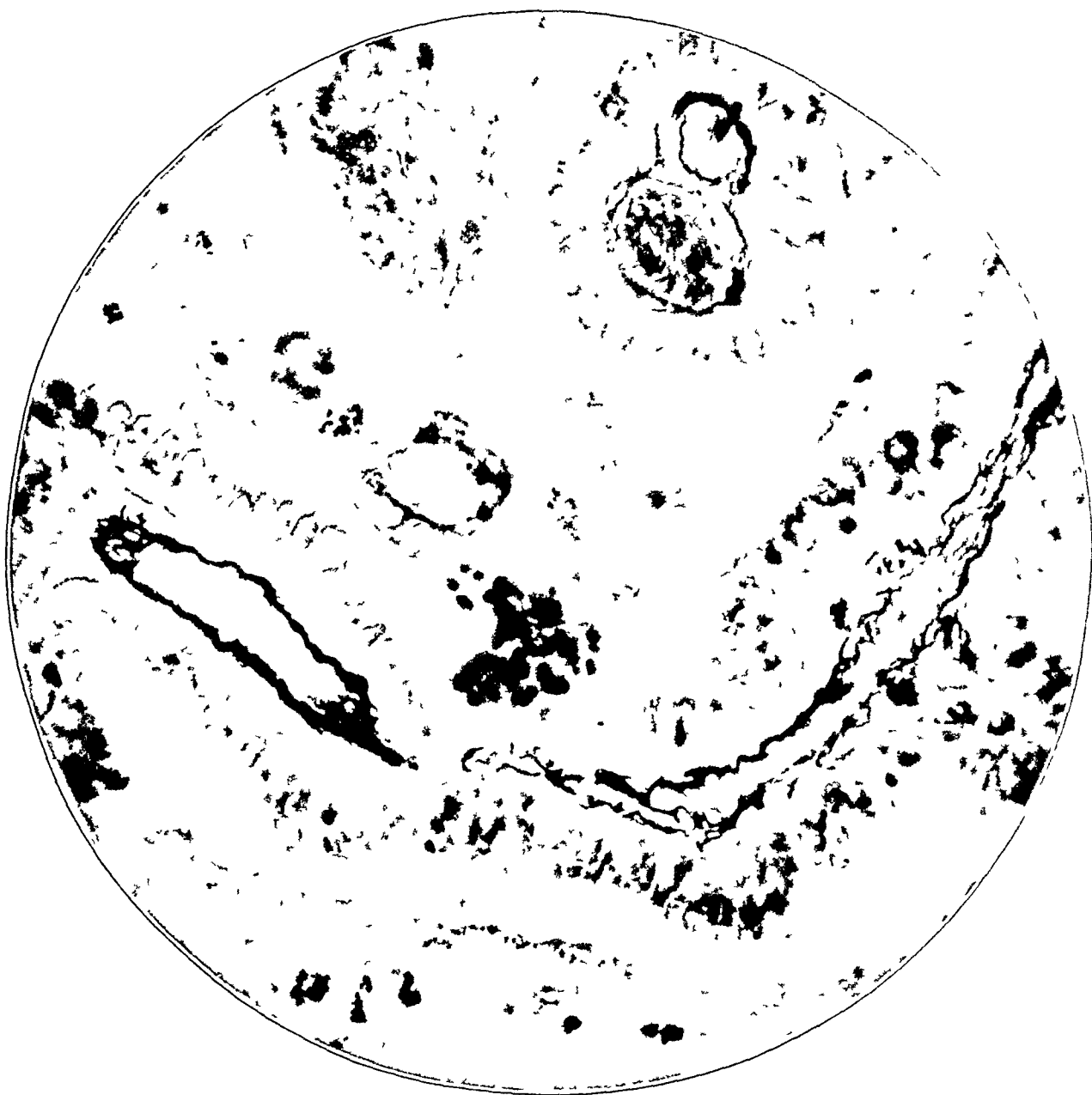


Fig 3—Perivascular orientation of the tumor cells. There is no proliferation of the vascular elements. Laidlaw connective tissue stain, $\times 454$.

of the breast there were metastases only to the brain. Other structures commonly involved were (1) the lungs, (2) the liver, (3) the adrenal glands and (4) the pancreas. The structures less frequently involved were the axillary lymph glands (most of them had been previously removed or treated with roentgen rays), heart, stomach, colon, ovaries, kidneys and thyroid.

There were 5 cases in which the primary malignant tumor was not located. Autopsies in 4 of these cases were limited to the head, in the fifth, though the autopsy was complete, there was no evidence of the primary growth or of metastases except in the brain. It seems likely that metastasis originated from a small bronchogenic carcinoma. In a few cases the primary bronchogenic tumor was very small.

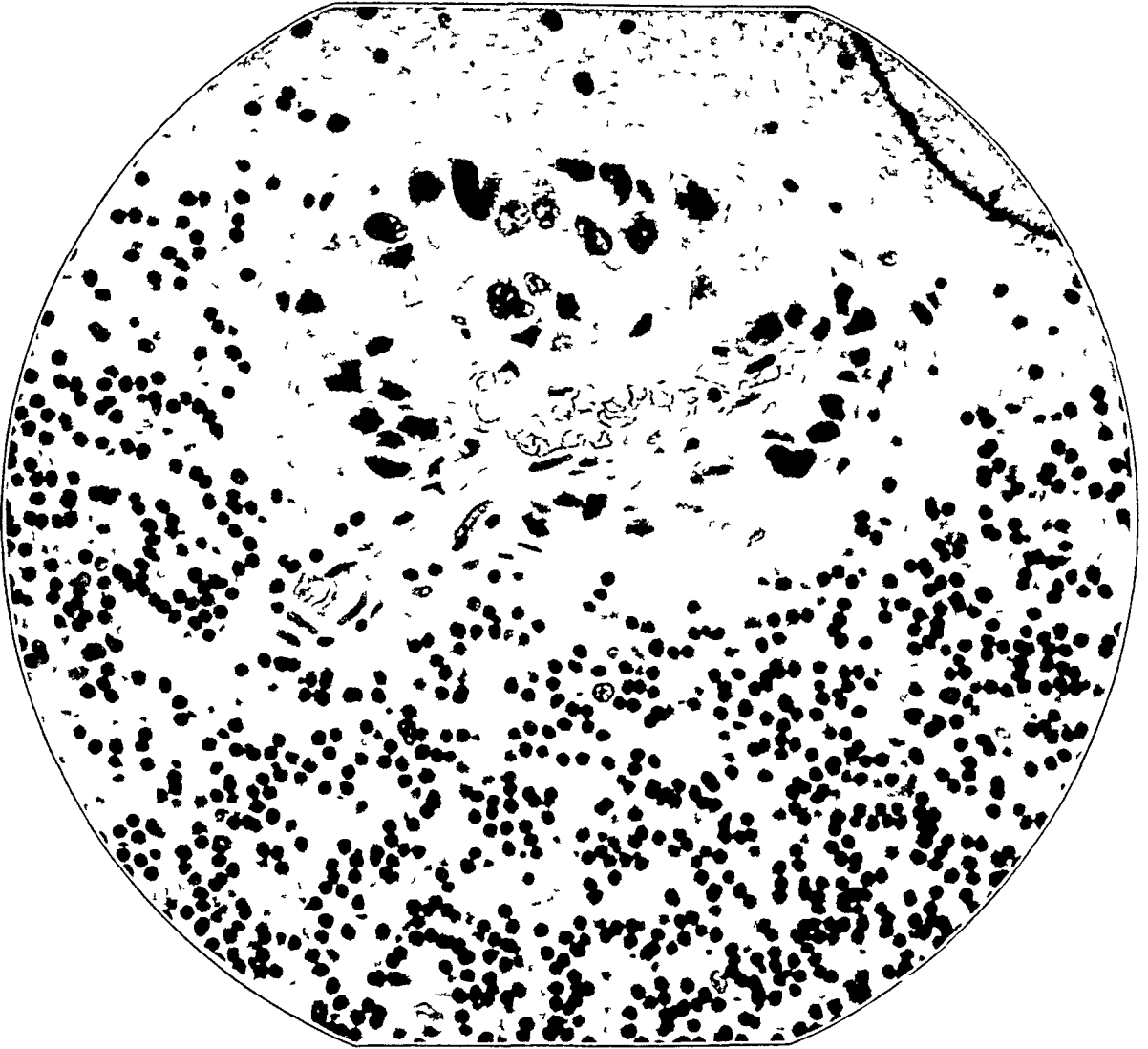


Fig 4—Cluster of metastatic carcinoma cells about a capillary of the cerebellum in an invaded area. Hematoxylin and eosin stain, $\times 384$

In the 1 case of carcinoma primary in the adrenal gland there were metastases to the kidney, lung and lymph glands as well as to the brain. In the case of carcinoma primary in the colon there were metastases to the lung and the cervical vertebrae as well as to the brain.

Microscopic Appearance of Tumors—The tumor cells of the metastatic nodules in the brain varied, as did the cell type of the primary tumor. In the majority of cases the cell types in the metastases were

identical with those of the primary growth. However in a few instances the cells of the cerebral metastases showed a definite histologic difference in size and arrangement from those of the primary tumor. The larger tumors showed a considerable degree of degenerative change centrally. At the margins of the nodules small clumps of tumor cells were seen invading the nearby parenchyma about the blood vessels (figs. 3, 4 and

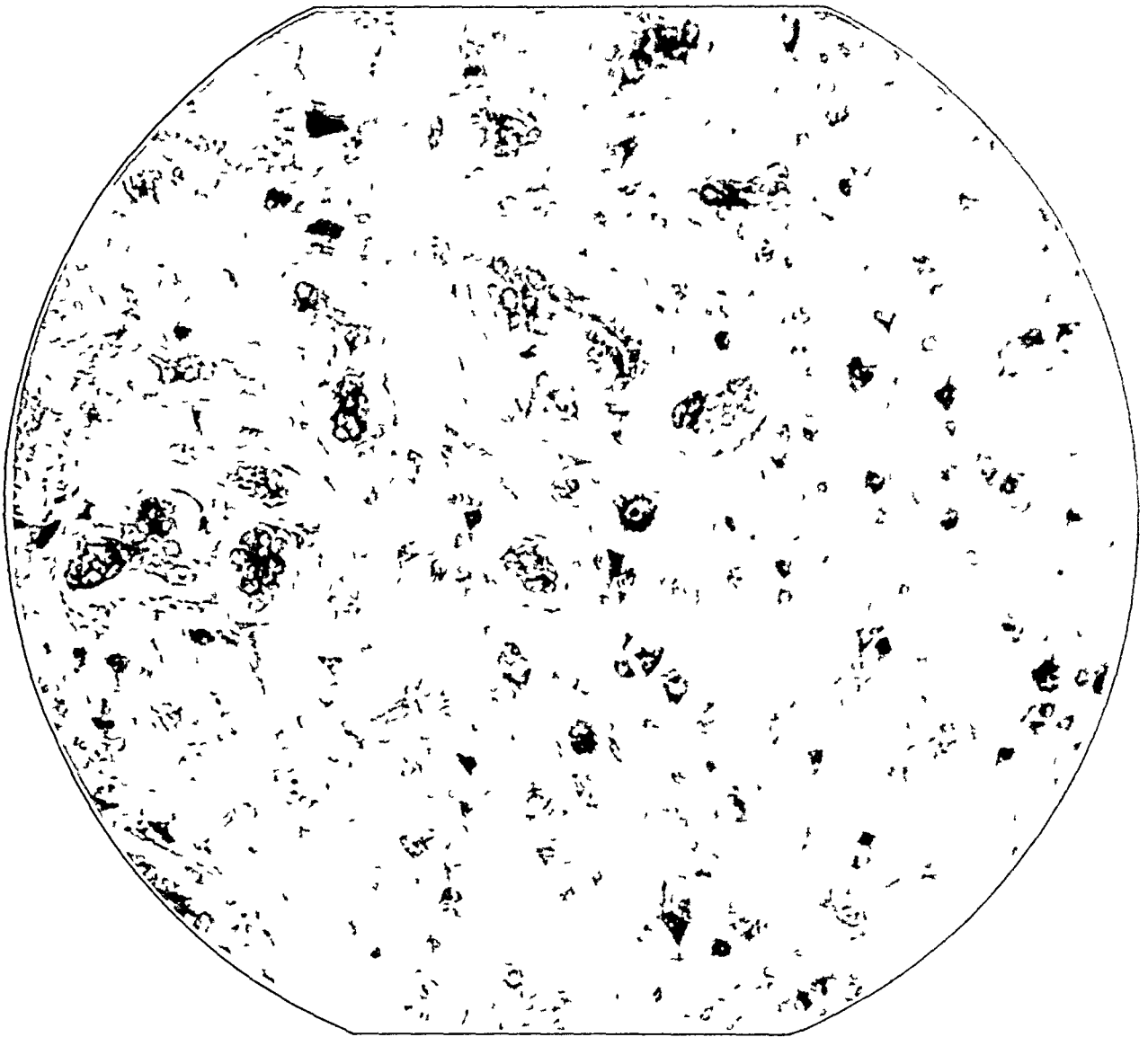


Fig. 5—Metastatic carcinoma infiltrating the cortex by perivascular growth. Note the degeneration of many ganglion cells between the projecting fingers of tumor tissue and the good preservation of some nerve elements away from the invaded area. Nissl stain, $\times 192$.

5) In a few cases tumor cells were observed within the lumen of the blood vessel. We believe that this tendency of the tumor cells to orient themselves about the blood vessels is one of the most striking features of cerebral metastatic carcinoma.²⁶

²⁶ Hassin, G. B., and Singer, H. D. Histopathology of Cerebral Carcinoma. Arch. Neurol. & Psychiat. 8: 155-170 (Aug.) 1922.

It should be stressed that the invaded brain tissue was totally destroyed and replaced by tumor tissue (fig 1). This may be important as an explanation of the fact that there is little evidence of increased intracranial pressure in cases of metastatic tumor. Whereas in cases of primary tumor of the brain the infiltration and moderate destruction of parenchyma result in an increase in intracranial contents, in cases

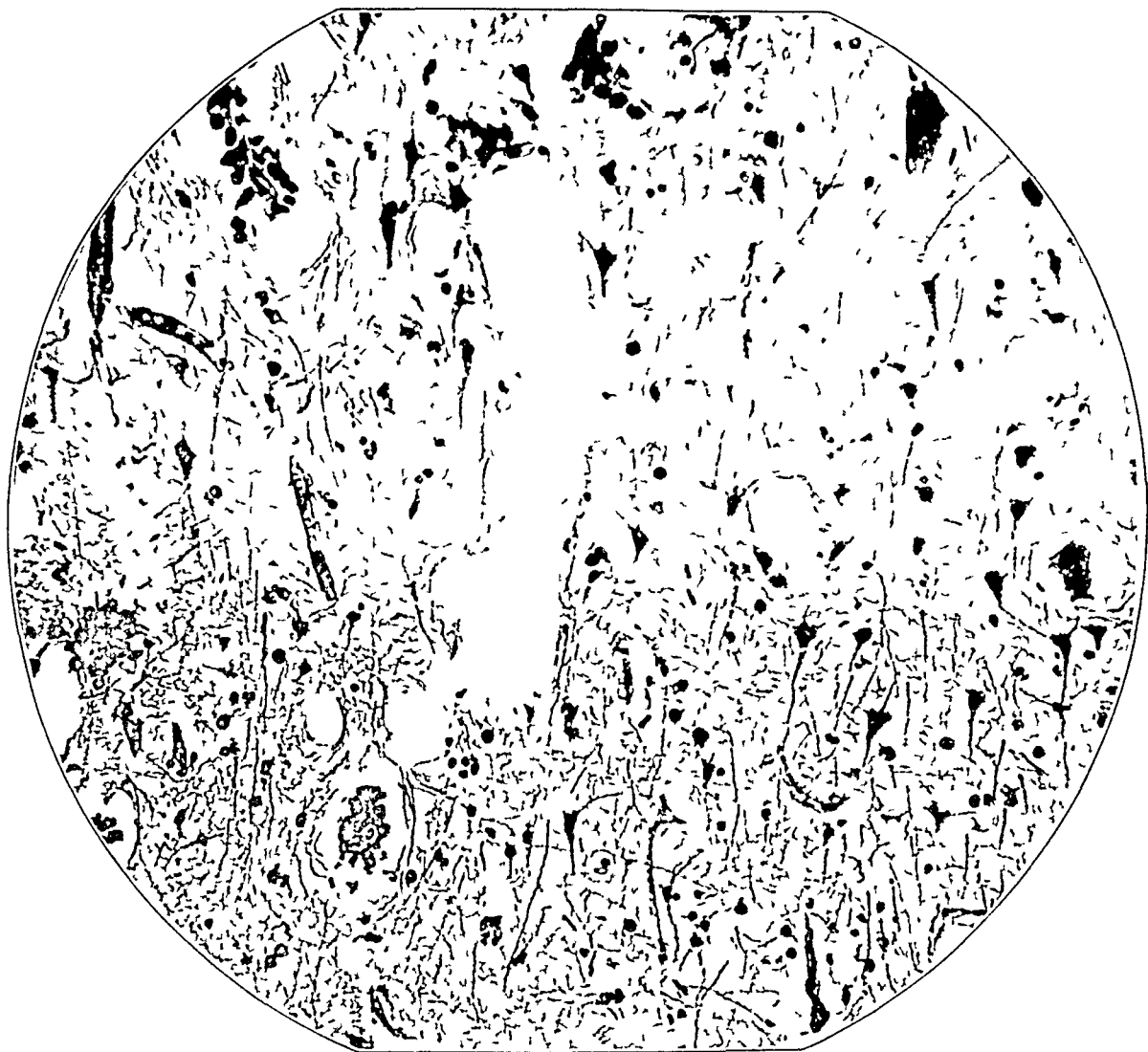


Fig 6—Spaces representing the position of the tumor nodules (perivascular). The photomicrograph shows the preservation of neurofibrillae in the heart of the invaded zone, although many are degenerated. The neighboring tissue is well preserved. Bielschowsky stain, $\times 192$.

of metastatic tumor, the complete destruction of the parenchyma and its replacement by neoplastic tissue suggest that there is less increase in intracranial contents, and therefore less increase in intracranial pressure in most cases.

Microscopic Appearance of Surrounding Brain—At autopsy some of the larger metastatic nodules could be enucleated easily and appeared to be entirely removable. Microscopically, however, tumor cells were seen extending into the surrounding brain tissue in many instances. The greatest change appeared to be the edema of the surrounding brain tissue, with swelling of the glial cells, but for the most part the adjacent parenchyma was well preserved (figs 5 and 6). In most cases there was a considerable increase in the number of astrocytes in the brain tissue immediately surrounding the tumor (fig 2). Perivascular infiltration of polymorphonuclear leukocytes and lymphocytes appeared commonly.

TREATMENT

Treatment is directed toward making the patient as comfortable as possible. As has been mentioned, the usual methods of dehydration do not appear to relieve the headache to any great extent. In 3 of our cases relief from headache was obtained for a few weeks by this form of treatment.

Surigically, it does not appear warranted to do more than a subtemporal decompression. There have been numerous reports of relief from headache by this procedure. Nine of the 34 patients in our series were operated on. In 2 cases subtemporal decompression was done with relief from headache, but both patients died in less than two weeks after the operation. A craniotomy was performed in 5 additional cases, death following in 4 instances in less than two weeks. One additional patient was thought to have a subdural hematoma because a trauma to the head precipitated his symptoms. Trephines of the skull and ventriculograms failed to disclose hemorrhage. The patient died seven days later. A ventriculogram was taken of another patient and his condition became much worse. These few reports seem to indicate that patients with intracranial metastatic tumor do not stand well even the simplest neurosurgical procedures. Seven of the 9 patients operated on died within two weeks after the operation. It seems doubtful, therefore, whether any operative procedure is advisable.

In our series 1 patient with severe headache was relieved by roentgen therapy. This form of treatment may be worth at least a trial.

There is considerable variance of opinion as to operative treatment of patients with carcinomatous metastases, particularly when it is thought that the metastatic lesion in the brain is single. Oldberg²⁷ has reported 2 cases in which the postoperative period of survival was more than two years and another in which it was eight months. His experience has led him to advocate operation under favorable conditions.

27 Oldberg E. Surgical Considerations of Carcinomatous Metastases to Brain, J A M A 101 1458-1462 (Nov. 4) 1933

Fried and Buckley¹⁷ favored operative treatment because it prolonged the lives of 4 of their patients for five months, seven months, two years and seven years, respectively. Five other patients died within two weeks after operation. Cushing,⁹ Giant,²² Elkington,¹⁰ Bunts²⁴ and others have favored a less radical procedure, such as decompression for relief from intracranial pressure, provided any operative procedure is indicated. In our opinion operation is indicated only for patients suffering pain from an associated increase in intracranial pressure. Decompression may afford temporary palliation of symptoms in such cases and appears to be indicated, provided the general health of the patient is such that at least a few months of life are to be expected. Most of the reports in the literature show that removal of a metastatic nodule from the brain, even though it is single, does not greatly prolong life.

CONCLUSIONS

1 Bronchogenic and mammary carcinoma commonly metastasize to the brain

2 The primary carcinoma in cases of cerebral metastasis is most commonly in the lung or breast. In our series of 100 cases there were 65 in which the primary tumor was so located.

3 A bronchogenic carcinoma often manifests its effects by cerebral metastasis before there are any pulmonary signs.

4 Carcinoma with cerebral metastases is not uncommon in persons less than 40 years of age. In our series it occurred in 27 of 100 cases.

5 The disease occurs predominantly in male patients, in the ratio 32:1, provided the cases of primary carcinoma of the breast are excluded.

6 Symptoms of metastasis are usually of short duration before the patient becomes seriously ill.

7 Gradual onset of intracranial symptoms in cases of metastatic intracerebral carcinoma, according to this study, is infrequent (17 per cent). The onset occurred suddenly in 36 of our 100 cases.

8 Patients with metastatic cerebral tumor do not tolerate surgical procedures well. The average duration of life from the time of the first neurologic symptom until death was three and six-tenths months for the 32 persons who died while under our care. The survival period was much shorter for those who were operated on.

9 Mental alterations may occur. Alterations of varying degree were present in 50 per cent of the patients studied, exclusive of those observed during the few days preceding death.

10 Severe headache may be an outstanding symptom. It may or may not be associated with papilledema.

11 Signs of chronic debilitating disease may be absent. They were lacking in 40 per cent of the cases in this series.

12 Abnormality of the spinal fluid is a prominent finding. It occurred in 70 per cent of the cases in which the spinal fluid was examined.

13 Roentgenographic erosion of the sella turcica may be present. In this series it was not uncommon in spite of the supposedly short duration of the cerebral metastases.

14 Encephalographic and clinical studies may localize one of the metastatic masses, which is usually the largest, and may fail to show the presence of other, smaller nodules.

15 Even after metastasizing to the brain, bronchogenic carcinoma may not appear as such on roentgenograms of the chest.

16 Metastatic cerebral tumors may be single or multiple. Multiple tumors were observed in 20 brains removed at autopsy, single nodules, in the remaining 14 cases.

17 In practically all cases of cerebral metastasis there are metastases to other organs.

18 Cerebral disease in addition to the metastases may be present. In 1 of our cases a cholesteatoma was observed in the cerebellopontile angle at autopsy, and in 3 syphilis of the central nervous system was evidenced by positive Wassermann reactions of the spinal fluid.

19 A primary cerebral neoplasm may be present with a carcinoma elsewhere in the body. We have observed 2 cases, not included in this series, in which a cerebral glioblastoma multiforme was verified pathologically and was associated with a prostatic carcinoma without metastases. Cases in which there were cerebral metastases from the prostate tissue were lacking in our series.

20 Surgical removal of single metastases in a few cases may prolong life for months, or even for several years, such cases, however, form a small percentage of those in which operation is done, most of the patients dying shortly after craniotomy.

21 Subtemporal decompression often relieves the headache and affords great comfort to the patient and his relatives.

22 When craniotomy is to be performed roentgen studies of the chest should be made, regardless of the age of the patient.

Permission to use the autopsy material described in this paper was granted by the department of pathology, Columbia University College of Physicians and Surgeons.

PRIMARY CARCINOMA OF THE LIVER

TUMOR THROMBOSIS OF THE INFERIOR VENA CAVA AND RIGHT AURICLE

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The comparative rarity of primary carcinoma of the liver is shown by the figures of Rowen and Mallory,¹ who found 7 instances of this condition in 6,506 consecutive autopsies. Orth² found 4 cases of primary carcinoma of the liver in 258 cases of hepatic cancer and in 713 cases of cancer of all types. Goldzieher and Bokay³ encountered this disease 18 times in 6,000 necropsies. Hansemann⁴ and Rindfleisch⁵ concluded from their studies that primary carcinoma of the liver represents about 0.5 per cent of all cancers.

Ewing⁶ stated that metastasis occurs infrequently. Of 163 cases of primary carcinoma of the liver studied by Eggel,⁷ 46, or 28 per cent, showed no extensions, and in 50, or 30 per cent, metastasis was limited to the branches of the hepatic or the portal veins. The lungs were the most frequent extrahepatic site of metastasis.

The great infrequency with which tumor thrombosis of the inferior vena cava occurs was shown by Simpson.⁸ In his study of this condi-

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1 Rowen, H. S., and Mallory, J. B. A Multinucleated Liver Cell Carcinoma, *Am J Path* **1** 677, 1925.

2 Orth, J. *Lehrbuch der speciellen pathologischen Anatomie*, Berlin, A. Hirschwald, 1887, p. 955, cited by Ewing, J. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1931, pp. 721 and 731.

3 Goldzieher, M., and von Bokay, Z. Der primäre Leberkrebs, *Virchows Arch f path Anat* **203** 75, 1911.

4 Hansemann, D. Ueber den primären Krebs der Leber, *Berl klin Wchnschr* **27** 353, 1890.

5 von Rindfleisch, H. Lebercirrhose und gewissen epithelialen Neubildungen der Leber, *München med Wchnschr* **48** 283, 1901.

6 Ewing, J. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1931, pp. 722-723.

7 Eggel, H. Ueber das primäre Carcinom der Leber, *Beitr z path Anat u z allg Path* **30** 506, 1901.

8 Simpson, W. M. Tumor-Thrombosis of the Inferior Vena Cava, with Four Additional Cases of Neoplastic Invasion, *Ann Clin Med* **3** 29, 1924.

tion, he was able to find but 78 cases in the literature up to 1924. In only 7 of this number was the condition due to primary carcinoma of the liver.

The rarity of tumor thrombosis of the inferior vena cava or the right auricle resulting from primary carcinoma of the liver is further shown by my survey of the literature, in which I found reports⁹ of 234 cases of primary carcinoma of the liver. In only 6 of this number was there thrombosis of the vena cava or right auricle.¹⁰ In 1 of these cases^{10d} the involvement was insufficient to produce any obstruction. In another^{10c} the tumor thrombus in the right auricle resulted from direct extension through the diaphragm and wall of the right auricle.

The difficulties encountered in the diagnosis of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava or right auricle or both of sufficient degree to produce obstruction caused me to analyze the 7 cases previously reported by Simpson and the 4 additional cases found in the literature and to report my study of an additional case.

REPORT OF A CASE

C. W., a Negro aged 35, a farm laborer, was admitted to the medical service of the Charity Hospital on Sept 6, 1936. His complaints were pain in the back and swelling of the extremities. Five weeks before admission, his left ankle began

9 Clawson, B. J., and Cabot, V. S. Primary Carcinoma of the Liver, *J. A. M. A.* **80** 909 (March 31) 1923. Griffith, J. P. C. Primary Carcinoma of the Liver in Infancy and Childhood, *Am. J. M. Sc.* **156** 79, 1918. Boyce, F. F., and McFetridge, E. M. Primary Carcinoma of the Liver, with Report of Twenty-Eight Additional Cases, *Internat. S. Digest* **18** 67, 1934. Martinez, J. A. Primary Carcinoma of the Liver. Description of an Unusual Case, *Lancet* **2** 1293, 1935. Smith, K. J. Primary Carcinoma of the Liver, *J. Lab. & Clin. Med.* **18** 915, 1932. Brines, O. A. Primary Tumors of Liver, *Am. J. Clin. Path.* **3** 221, 1933. Tull, J. C. Primary Carcinoma of the Liver. A Study of One Hundred and Thirty-Four Cases, *J. Path. & Bact.* **35** 557, 1932. Strong and Pitts^{10c}. Counseller and McIndoe^{10d}. Von Glahn and Lamb^{10b}. Williamson, C. S. Primary Carcinoma of the Liver, *M. Clin. North America* **8** 453, 1924. Friedenwald, J., and Fried, H. Primary Cancer of the Liver, *Am. J. M. Sc.* **168** 875, 1924. Fried, B. M. Primary Carcinoma of the Liver, *ibid.* **168** 241, 1924. Karsner, H. T. A Clinicopathological Study of Primary Carcinoma of the Liver, *Arch. Int. Med.* **8** 238 (Aug.) 1911. Milne, L. S. Primary Epithelial Tumor Growth in the Liver, *J. Path. & Bact.* **13** 348, 1909.

10 (a) Culpepper, A. L., and von Haam, E. Primary Carcinoma of the Liver with Extensive Metastasis to the Right Heart, and Tumor Thrombosis of the Inferior Vena Cava, *Am. J. Cancer* **21** 355, 1934. (b) Von Glahn, W. C., and Lamb, A. R. Primary Carcinoma of the Liver, *M. Clin. North America* **8** 29, 1924. (c) Strong, G. F., and Pitts, H. H. Primary Carcinoma of the Liver, *Arch. Int. Med.* **46** 105 (July) 1930. (d) Counseller, V. S., and McIndoe, A. H. Primary Carcinoma of the Liver, *ibid.* **37** 363 (March) 1926. (e) Fabyan, M. A Case of Primary Carcinoma of the Liver Supervening in a Cirrhotic Liver, *Bull. Johns Hopkins Hosp.* **18** 351, 1907.

to swell. The swelling was marked for several days. It always diminished and sometimes disappeared during the night. Shortly afterward the right foot began to swell. The patient continued his work until the day before admission, at which time edema of both extremities was very marked and extended about half way between the knee and the hip. Three weeks previous to admission and two weeks after the onset of edema, the pain in the back was noticed. It was in the right lumbar region and was constant and aching in character, but sometimes so severe as to permit no rest or sleep. It did not radiate and was not increased by postural changes. It was relieved, however, by sitting up. This symptom caused the patient to seek admission to the hospital. He had not been aware of fever. He urinated about ten times daily, with equal distribution between night and day. He had had gonorrhea and a penile sore twelve years before admission. The family, social and marital histories were irrelevant. He persistently denied that he had noticed any dyspnea. It may be emphasized that he had been doing hard farm work until the day before admission. He had walked five miles and worked until midnight twice a week in addition to his farm duties.

Physical Examination—The patient was well developed and well nourished. He did not appear acutely ill. There were no important abnormalities in the head, neck, lungs or heart. The blood pressure was 160 systolic and 98 diastolic. The liver was easily palpated about 4 cm. below the right costal margin in the midclavicular line, at about which point a distinct notch or nodule was felt. The liver was firm, the edge was not sharp, and there was no tenderness. The abdomen was otherwise normal. The patient was not jaundiced. The rectum and the genitalia were normal. There was questionable tenderness of uncertain significance in the right costovertebral angle. There was marked pitting edema with shiny skin up to about 6 inches (15 cm.) above the knees. The temperature was normal on admission.

Laboratory Data—The urine contained a trace of albumin on three occasions. Results of microscopic examination were always normal. Examination of the blood showed the value for hemoglobin to be 90 per cent, the white cell count was 6,750 per cubic millimeter, with 17 per cent lymphocytes and 83 per cent polymorphonuclears. No malarial organisms or filarias were seen. The Wassermann reaction of the blood was strongly positive on two occasions. The urea nitrogen content of the blood was 35 mg. and the creatinine content 2.9 mg. per hundred cubic centimeters on the day before death. Roentgenograms of the chest showed no pathologic condition of the lungs, mediastinum or great vessels. A large liver shadow and elevation of the right dome of the diaphragm were seen. Antero-posterior and lateral roentgenograms of the spine showed no evidence of disease.

Course in Hospital—The patient was given complete rest in bed and was able to lie flat on his back or abdomen without dyspnea. After he had spent a week in bed the edema was much less, but never disappeared. His only complaint was backache. Although there was some general improvement, it was very slight. There were elevations of temperature to 99 F. and on several occasions to 100 or 101 F., but this was not continuous.

The patient was not aware of any significant loss of weight. Because of the history of a penile lesion, the positive Wassermann reaction and the hard, irregular liver, a diagnosis of gummas or syphilitic cirrhosis of the liver was considered, and he was given potassium iodide and bismuth medication. We were unable, however, to account for the marked dependent edema on this basis. Filariasis was considered, but no filarias were seen in either of two examinations of the blood,

one of which was made at night. Because of the possibility of a malignant retroperitoneal tumor compressing or invading the inferior vena cava, roentgenograms of the kidneys, ureters and bladder were made, but no abnormality of this sort was suggested by the findings. The patient was then transferred to the urologic service for retrograde pyelographic studies. While a slight urethral stricture was being progressively dilated as a preliminary procedure, his condition became much worse, and he was transferred back to the medical service.

Examination at this time, one month after admission, showed him to be orthopneic. The veins of the neck were engorged, and there was a marked increase in the size of the liver, which extended to the umbilicus and was very tender. There were moderate ascites and extreme edema of the lower part of the trunk, the scrotum, the penis and the lower extremities. In addition, slightly dilated veins were noted for the first time on the upper part of the abdomen and the lower aspect of the thorax on both sides. Pressure on the upper part of the abdomen, particularly over the liver, produced marked increase in the jugular engorgement. The patient complained of extreme backache, which required codeine or morphine for relief. From this point the course was rapidly downhill. Death occurred on October 25, forty-eight days after admission. Autopsy was performed by Dr. J. R. Schenken, of the department of pathology, thirty-six hours after death.

The anatomic diagnosis was primary carcinoma of the liver (of liver cell type) with widespread hepatic involvement (weight of liver, 4,000 Gm) and extensive tumor invasion of branches of the hepatic veins, tumor (carcinomatous) thrombus of the inferior vena cava and right auricle (filled) and tumor embolism of the pulmonary arteries, cirrhosis of the liver, bilateral edema of the lower extremities, and ascites, with serosanguineous fluid.

In spite of the numerous findings which suggested congestive heart failure at the end, the clinical course was definitely against such a diagnosis. The marked edema of the legs on admission with no shortness of breath or jugular distention deserved further emphasis in this connection. The pulse rate was about 84 much of the time, even during the last few days. The dilatation, though slight, of the veins of the upper part of the abdomen and the lower part of the thorax pointed to obstruction of the inferior vena cava as the cause of edema of the lower portion of the body. This, however, did not explain the orthopnea or the jugular distention. Nor would it account for the increase in size or the tenderness of the liver unless the obstruction was at or above the diaphragm.

The extreme backache of which the patient complained and because of which he sought admission to the hospital was not explained clinically. Metastatic spinal disease was ruled out by roentgenograms. The possibility of an abdominal aneurysm with spinal erosion was ruled out in the same manner. The fact that the pain was relieved, at least in the beginning and to a certain extent at the end, by the patient's assuming a sitting or standing position leads one to suggest as a possible explanation that the pain was due to the pressure of the large and heavy liver against the spine.

Pleasants¹¹ called attention to lumbar pain as a feature of thrombosis of the vena cava of inflammatory and tumor origin, but he did not explain the mechanism of the pain.

The possibility of the pain being due to increased pressure in the renal veins, with renal congestion, is perhaps worth consideration.

The final clinical diagnosis rested between tumor thrombosis (primary origin unknown) of the inferior vena cava and syphilitic cardiovascular disease with congestive heart failure.

COMMENT

I have found in the literature 11 instances of tumor thrombosis of the inferior vena cava or the right auricle or both which resulted from primary carcinoma of the liver. To this list I am adding a case.

I have arranged my analysis of the complaints, physical findings and laboratory data (including autopsy observations) in tables 1, 2 and 3, respectively. No clinical data are available on the cases reported by Rowen and Mallory¹ and by Reynaud¹².

Seven of the cases (6 to 12, inclusive, in the tables) have been previously reviewed by Simpson⁸. My new case is included in the tables as case 5.

The difficulty with which primary carcinoma of the liver with tumor thrombosis of the inferior vena cava is diagnosed is evidenced in table 1. In no instance was the diagnosis made correctly. The fact that a clinical diagnosis was not given in 9 of the 12 cases is ground for the belief that the clinical diagnosis was wrong. In my case (case 5) the possibility of tumor thrombosis of the inferior vena cava was suspected, and as it is well recognized that malignant tumors of the kidney are the principal source of such thrombosis, the patient was prepared for a urologic examination, when he suddenly became much worse and died shortly thereafter.

The suspicion of obstruction of the inferior vena cava was later more tangibly supported by the development of dilatation of the superficial veins of the anterolateral portions of the thorax and abdomen. Simpson⁸ has called attention to the infrequent occurrence of this classic diagnostic criterion of thrombosis of the inferior vena cava. Dilatation of the superficial veins was not present in any of the 4 cases in his own series and was present in less than one half the cases he reviewed. Of the 4 cases of primary carcinoma of the liver reviewed by me (in

11 Pleasants, J. H. Obstruction of the Inferior Vena Cava, with a Report of Eighteen Cases, *Johns Hopkins Hosp. Rep.* **16** 343, 1911.

12 Reynaud, P. Cancer du rein droit. Presence de la matière cancéreuse dans la veine rénale, dans la veine cave et dans la vessie, *Bull. Soc. anat. de Paris* **8** 60, 1833, cited by Simpson⁸.

Case	First Symptoms	Swelling of	Jaundice	Other Complaints	
				Abdominal Swelling	Edema of Legs
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

Case	Age	Sex	Race	First Symptoms	Jaundice	Other Complaints				Clinical Diagnosis	Stay in Hospital	Length of Illness	Author
						Abdominal Swelling	Edema of Lower Extremities	Pain	Shortness of Breath				
1	50	M	Negro	Swelling of the ankles (progressive)	Slight at autopsy	Present	Present (entire lower limbs and abdominal wall)	Dull pain in region of stomach	Marked for 3 weeks prior to admission	Not mentioned	35 days (death)	5 weeks	Culpepper and von Haum
2	73	M	White	Swelling of legs at night	Present (late)	Present	Present	Constant dull epigastric pain	Present	Present and progressive	Arteriosclerotic heart disease with decompensation	5 weeks	Culpepper and von Haum
3	51	M	White	Swelling and discomfort in abdomen	Slight, but increased before death	Present	Present from beginning		Present	Present and progressive	Diabetes (20 years) otherwise not mentioned	6 weeks	Von Glahn and Lamb
4	62	M	Negro	Long illness with weakness and swelling of abdomen	Not mentioned	Present	Not mentioned		Dyspnea on exertion	Present	Not mentioned	11 days (death)	Von Glahn and Lamb
5	35	M	Negro	Swelling of ankles	None	Developed in hospital	Present (thighs and abdominal wall)	Lumbar region of back, severe	Not mentioned	Present 9 months	Not given	7 weeks	Von Glahn and Lamb
6	51	M	White	Swelling of lower extremities	None	Present	Present		None on admission orthopnea began in hospital	None on admission	Tumor thrombus of inferior vena cava vs syphilitic aortitis with congestive heart failure	9 months	Huban
7	25	M	White	Cough	Swelling of legs	Present	Present					5 weeks	Gregory (present case)
8	19	M	White	Progressive edema of legs	Present	Present	Present		Present				
9	51	F	White	Weakness, dyspnea, swelling of legs	Present	Present	Present		Present				
10	Clinical data not available								Present				Challier and Gurin
11	70	F	White	Swelling of lower extremities	None	Marked (thighs)	Present				5 months		Gull
12	13	M	White	Chills, swelling of lower extremities	Present	Present	Present				2 weeks		Jancura
						Present (also abdominal wall and scrotum)					2 months		McLelland
											2 weeks		Reynard Sternberg
											2 months		Vincent

TABLE 2—*Physical Findings in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle*

Case	Liver	Ascites	Cardiac Signs	Edema of Lower Extremities	Edema of Upper Extremities	Collateral Circulation	Veins of Neck	Cyanosis	Temperature, Degrees F	Spleen
1	Not palpated, owing to abdominal distention, but enlarged on percussion	Present	Slightly enlarged (?) dyspnea, engorged veins of neck	Massive	Not mentioned	None mentioned	Distended, pulsating	Lips and Nose	98.4	Enlarged on percussion
2	Halfway to umbilicus hard and firm	Present	Enlarged (?)	Present	Not mentioned	None mentioned	Not mentioned	Not mentioned	98.6	Just felt
3	Two inches below right costal margin	Present	None recorded	Present	Not mentioned	Few dilated veins over lower part of thorax	Not mentioned	Not mentioned	Afebrile	Not felt
4	Five inches below right costal margin nodular	Not mentioned	Not mentioned	Present (autopsy)	Not mentioned	One prominent superficial abdominal vein	Not mentioned	Not mentioned	Not given	Not mentioned
5	To umbilicus	Present	Orthopnea jugular engorgement	Massive	None	Present on both sides of upper part of abdomen and lower part of thorax	Engorged	Not observed	Occasionally 100.1	Not felt
6		Present	None	Present		None				
7		Present	None	Present		Present				
8		Present	None	Present		None				
9		Present		Present		None				
10	Clinical data not available									
11		None	None	Present		None				
12		Present	None	Present		Present superficial				

TABLE 3—Laboratory Findings in Twelve Cases of Tumor Thrombosis of Inferior Vena Cava and/or Right Auricle

Case	Urine	Blood*	Ascidic Fluid	Thrombosis of Vena Cava	Invasion of Hepatic Veins	Invasion of Portal Branches	Retrograde Thrombosis	Thrombus in Right Auricle	Pulmonary Tumor Emboli	Other Metastases	Collateral Circulation	Other Pathologic Conditions	Histologic Type of Primary Tumor	Heart	Liver, Gm	Spleen
1	Albumin, granular casts	Hb 60%, R B C 3,990,000, W B C 15,200, Wass (—)	1,500 cc., dark brown	Present, occluded	Present	Present	Blood clot extending to common iliac veins	Tumor thrombus	Few	Retroperitoneal and hepatic ligament	No increase mentioned	Portal cirrhosis, pericardial effusion	Hepatoma	300 Gm., valves normal	2,900 Gm	400 Gm
2	Hyaline casts	R B C 4,900,000, W B C 9,600, Wass (—)	2,400 cc., turbid	Present, occluded	Present	Present	None	None	Present	None	No increase mentioned	Cirrhosis, hemosiderosis	Diagnosis not made, hepatoma likely	Weight not given	1,670	Not mentioned
3	Few hyaline casts	Hb 105%, R B C 5,000,000, W B C 15,200, Wass (—)	Character and amount not mentioned	Present, occluded	Present	Present	None	None	None	None	Increased in hepatic ligaments and peritoneal surface of diaphragm	Cirrhosis of liver, pneumonia	Hepatoma	Condition not mentioned	1,300	Moderately enlarged
4	Data not given	Data not given	3 liters, straw colored	Complete occlusion	Present	Present	None	None	Present	Lungs	Not mentioned	Liver cirrhosis, esophageal varices	Not mentioned	Coronary sclerosis	1,300	Not enlarged
5	Trace of albumin, microscopical examination normal	Hb 90%, W B C 6,750, L 17%, P 83%, no malarial organisms, no filarias, Wass 4 plus	800 cc serous, gelatinous fluid	Present	Present to marked degree	Present	Not mentioned	Present, almost filling right auricle	Present	None	Not mentioned	Cirrhosis of liver	Hepatoma	150 Gm	1,000 Gm	250 Gm
6	Albumin		Present	Present	Present		Present, entire inferior vena cava auricle	Large distending right auricle					Not differentiated			
7			Present	Present	Present		Extended to renal veins				Azygos and intercostal veins		Not differentiated			
8			Present	Present	Present								Hepatoma			
9	Albumin		Present	Present	Present	Present	Extended to common iliac veins	Present								
10			None	Present	Present		Tumor thrombus to renal veins	Present			None		Not given			
11			Present	Present	Present		blood thrombus to femoral veins	None					Not given			
12	No albumin		Present	Present	Present								Not differentiated			

* In the table "Hb" indicates hemoglobin content, "R B C," red blood cells "W B C," white blood cells, "Wass," the Wassermann reaction "L," lymphocytes, and "P," polymorphonuclears

addition to Simpson's cases), this sign was noted to a slight degree in 2 In 5 of the 11 cases on which I have clinical data dilated superficial veins of the abdomen or thorax were observed This appears to indicate that the incidence of superficial venectasis is approximately the same in thrombosis of the vena cava from carcinoma of the liver as in tumor thrombosis of the inferior vena cava from other sources

Most writers have called attention to the rapidly fatal course of primary carcinoma of the liver The cases reviewed by me confirm their observations With the exception of case 4 (reported by Fabyan), in which the patient had probably had hepatic cirrhosis for most of the nine months of his sickness, the average duration of symptoms prior to admission to the hospital was five to six weeks, and the average stay in the hospital before death was twenty-eight days in the 4 cases on which I have sufficient data

My primary interest in the study of this subject is in defining the criterion for the diagnosis of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava, the right auricle or both I have found no instance in which tumor thrombosis of the right auricle resulted from primary carcinoma of the liver in the absence of thrombosis of the inferior vena cava unless such thrombosis took place by extension through the diaphragm and the wall of the auricle ^{10c}

Although small pulmonary emboli of tumor cells were commonly observed, I found no instance in which these emboli caused sudden death, as Judd and Scholl ¹³ reported in cases of malignant renal tumors, particularly at or immediately after operative procedures

The two uniformly occurring complaints were swelling of the lower extremities (usually progressive) and swelling of the abdomen Likewise, edema of the lower extremities and ascites were the only signs uniformly present

I believe it to be significant that dependent edema was among the first symptoms noted in all but 1 case (case 4) As I have observed, it seems likely that the primary complaints of the patient in this case were due to cirrhosis of the liver with portal decompensation and that the signs of primary carcinoma of the liver were superimposed as late manifestations The initial dependent edema is probably not to be explained on the basis of tumor thrombosis of the inferior vena cava alone ¹⁴ The development of this edema in the absence of any short-

¹³ Judd, E S, and Scholl, A J Thrombosis and Embolism Resulting from Renal Tumors, *J A M A* **82** 75 (Jan 12) 1924

¹⁴ (a) Winternitz, M C Primary Carcinoma of the Liver, *Johns Hopkins Hosp Rep* **17** 143, 1916 (b) Bejan, J, and Cohn, M Sur la ligature de la veine cave inferieure, étude experimentale, *Rev de chir* **43** 302, 1911 (c) Cole, H P Laceration of the Inferior Vena Cava Repaired by Suture, Recovery, *Ann Surg* **66** 43, 1917 Footnotes 8 and 10 c

ness of breath is an argument against a diagnosis of heart disease. It is essential, therefore, when patients with such edema are seen late and have some shortness of breath that a complete history of the sequence of events be obtained.

This point is well illustrated by cases 1, 2 and 5, particularly cases 1 and 5, in which there was marked edema of the lower extremities for two and four weeks, respectively, before the onset of any respiratory difficulty. Culpepper and von Haam^{10a} concluded that thrombosis of the right auricle occurred before thrombosis of the vena cava in their case. From an analysis of their clinical data, I believe that thrombosis of the vena cava occurred before the right auricle.

Dyspnea of marked degree was present in only 3 patients (1, 5 and 8). Some dyspnea on exertion was present in patients 2 and 3. In patients 1, 5 and 8, who had severe dyspnea (orthopnea), thrombosis of the right auricle was observed. This was observed also in case 6, no statement, however, was made regarding dyspnea. The correlation between extreme dyspnea and auricular thrombosis, although not complete, is high. From this and theoretic considerations, I believe that it is probably an important point. Therefore, if malignant thrombosis of the inferior vena cava is probable, the sudden onset, after weeks of dependent edema, of severe dyspnea or orthopnea, marked increase in the size of the liver, ascites and jugular engorgement is strong evidence to support the clinical diagnosis of thrombosis of the right auricle.

Jaundice was present in 4 of the 11 cases in which there were clinical data: to a slight degree in 3 cases¹⁵ and to a moderate degree before death in 1 case. In the latter, the jaundice was associated with the presence of bile in the urine. Smith¹⁶ has reported a much greater incidence of jaundice, observing it in practically all of 23 cases of primary carcinoma in which the diagnosis was proved at autopsy.

Reference to table 1 will show that pain is an inconspicuous part of the general picture of carcinoma of the liver with obstruction of the vena cava. As I have pointed out, pain in the lumbar region of the back was severe in my case (case 5) and was the immediate cause of the patient's seeking medical attention.

Judging from the data in cases 1 to 5, moderate to marked enlargement of the liver is present in primary carcinoma with obstruction of the vena cava. As I have pointed out, given a large liver and dependent edema as the only complaints or signs, the sudden marked increase of edema, with appearance of ascites and shortness of breath, should suggest thrombosis of the right auricle superimposed on thrombosis of the inferior vena cava.

15 Rowen and Mallory¹ Orth² Culpepper and von Haam^{10a}

16 Smith, K. J. Primary Carcinoma of the Liver, *J Lab & Clin Med* 18:915. 1933

Von Glahn and Lamb^{10b} expressed the opinion that when the diagnosis rests between cirrhosis with portal decompensation and primary carcinoma of the liver, the presence of a large liver with ascites is in favor of the latter. They made the point that hepatic cirrhosis is seldom associated with ascites when the liver is still large.

The laboratory data (table 3) appear to offer no information of differential diagnostic value. The urine in 4 of our cases showed albumin. Simpson⁸ called attention to the infrequency of abnormal urinary findings even in the presence of complete thrombosis of the vena cava above the renal veins. He explained this as being due to the ease with which the renal capsular collateral veins reestablish adequate venous circulation. In my case the urea nitrogen content of the blood was 35 mg and the creatinine content 2.9 mg per hundred cubic centimeters. The kidneys weighed 260 and 300 Gm and showed marked congestion, which was probably the cause of the slight nitrogen retention.

In view of the fact that malignant tumors of the adrenal glands, kidneys, testicles and liver with tumor thrombosis of the inferior vena cava and/or right auricle may present the end picture of edema, ascites, shortness of breath and enlargement of the liver, is there any means by which one may differentiate primary carcinoma of the liver with thrombosis of the vena cava from these other conditions? I believe that this is possible. Although Simpson⁸ has shown that of the four common causes of tumor thrombosis of the inferior vena cava carcinoma of the liver ranks third (it formed only 10 per cent of his series), it seems likely that careful attention to the details of development of symptoms may make it possible to differentiate primary carcinoma of the liver with tumor thrombosis of the vena cava from the other conditions causing tumor thrombosis of the vena cava. It is unlikely that tumors of the testicles producing thrombosis of the vena cava will present any problem, because of the ease with which these organs may be examined.

Table 1 reveals that except in case 4, in which the patient had been ill for months, probably as a result of the cirrhosis, swelling of the lower extremities was invariably the first or among the first symptoms noted. In Simpson's review,⁸ edema of the lower extremities was noted as the initial symptom in only 5 of 32 cases of thrombosis of the vena cava from renal malignant tumor, in none of 13 cases of malignant tumors of the testis with thrombosis of the vena cava and in none of the cases of malignant tumors of the adrenal glands or pancreas producing obstruction of the vena cava. On the other hand, edema of the lower extremities was the first symptom in all 6 cases of carcinoma of the liver on which clinical data were recorded by Simpson.

Numerous authors, including Simpson⁸ Winternitz,^{11a} Fabian^{10c} Bejan and Cohn,^{14b} Cole^{14c} and Judd and Scholl,¹³ have called attention to the mildness or absence of circulatory disturbance in the lower extremities with marked obstruction of the vena cava. Judd and Scholl reported 3 cases of malignant tumors of the kidney filling the entire inferior vena cava, with no edema. Likewise, Woodruff and Levine¹⁷ reported a case of hypernephroid carcinoma of the kidney with tumor thrombosis of the entire vena cava and of the right auricle in which the disease ran its entire course without any edema of the lower extremities. There was, however, 1,500 cc of fluid in the abdomen at postmortem examination.

In none of the reported cases of primary carcinoma of the liver with thrombosis of the vena cava has the patient failed to show edema of the lower extremities. As has been noted, this was almost uniformly the first symptom or sign which developed. I believe the explanation for this phenomenon lies in the disturbance of one of the main collateral systems when thrombosis of the vena cava results from primary carcinoma of the liver.

Simpson,⁸ among others, has pointed out that renal function does not suffer as a result of occlusion of the vena cava above the renal veins. Although it is difficult to prove, it seems likely that edema and ascites, particularly the latter, do not develop until the thrombus reaches the level of the hepatic veins.

If this is true, it is easy to understand why edema of the lower limbs is so constantly observed as the first manifestation of thrombosis of the vena cava from primary carcinoma of the liver. The circulation may be obstructed by thrombosis of the hepatic veins, which is widespread in carcinoma of the liver, and the patient may not show edema early, as is usually the case in cirrhosis with portal obstruction. Likewise, as has been pointed out, the inferior vena cava anywhere below the hepatic veins may be thrombosed without producing edema. It appears likely that the portal system offers one of the means of collateral return. If, however, the hepatic veins are already occluded, or partly so, by tumor thrombosis, the thrombosis of the vena cava developing from this would more easily produce edema as a result of the portal system's failure to act as a collateral.

SUMMARY

The literature on primary carcinoma of the liver with respect to tumor thrombosis of the inferior vena cava and the right auricle is reviewed. The 7 cases previously reported by Simpson, 4 additional

¹⁷ Woodruff, L. W., and Levine, V. Hypernephroid Carcinoma of the Kidney, *J. A. M. A.* **106** 1544 (May 2) 1936.

cases found in the literature and a case of my own, reported here, have been studied particularly from the standpoint of the differentiation of primary carcinoma of the liver with thrombosis of the inferior vena cava and right auricle from tumor thrombosis of the inferior vena cava associated with malignant neoplasms of the kidneys, adrenal glands, testicles or pancreas

CONCLUSIONS

Tumor thrombosis of the inferior vena cava and/or right auricle is a rare complication of primary carcinoma of the liver. It occurred in 5, or 2.1 per cent, of 234 cases.

Dilatation of the superficial veins of the abdomen or thorax occurred in approximately 50 per cent of cases of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava.

The extreme pain in the lumbar portion of the back which was observed in my patient and was also noted by Pleasants¹¹ may possibly be explained by the marked passive congestion of the kidneys (weight, 260 and 300 Gm.).

Edema of the lower extremities was the first or among the first symptoms or signs noted in 11 of 12 cases of thrombosis of the vena cava from primary carcinoma of the liver which I studied. In Simpson's it occurred as an initial symptom in only 5 of 32 cases of renal malignant tumor, in none of 13 cases of malignant tumor of the testis and in none of the cases of malignant tumors of the adrenal glands or pancreas associated with tumor thrombosis of the inferior vena cava.

Marked invasion of the hepatic veins with tumor thrombus interferes with, if it does not actually prevent action of, the portal circulation as an important collateral return from the lower part of the body when the inferior vena cava becomes occluded with tumor. This is offered as an explanation for the almost uniform occurrence of edema of the lower extremities as an initial symptom of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava. This is in contrast to the extremely low incidence of edema of the extremities as an initial symptom of other malignant growths associated with tumor thrombosis of the inferior vena cava.

Edema of the lower extremities as an initial symptom not associated with shortness of breath or increased venous pressure but associated with a large liver is suggestive evidence of primary carcinoma of the liver with tumor thrombosis of the inferior vena cava.

The occurrence of orthopnea, marked increase in the venous pressure, sudden increase in edema of the extremities and the scrotum and sudden increase in the size and tenderness of the liver in a patient who presents reasonable evidence of tumor thrombosis of the inferior vena cava should be interpreted as good evidence that a tumor thrombus has formed in the right auricle.

THIOCYANATE DERMATITIS

REPORT OF A CASE

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The ability of the thiocyanates to lower the blood pressure was observed as early as 1903 by Pauli,¹ but the drugs were not introduced in the treatment of hypertension until 1924, by Westphal.² Their use has been limited, however, because of the toxic effects frequently produced. In 1932 Goldring and Chasis³ reported the toxic symptoms which occurred in 13 of 50 patients treated for hypertension with thiocyanate. These symptoms consisted of muscular fatigue, nausea and vomiting, mental confusion, hallucinations and motor aphasia. They also reported 2 deaths, preceded by delirium, convulsive twitchings and coma. They pointed out that some persons show a distinct susceptibility to the drug.

In 1926 Takacs⁴ reported the first case of dermatitis due to thiocyanate. This was a papular eruption which occurred after the ingestion of 1 Gm of potassium thiocyanate daily for nine days. Since that time there have been reported numerous cases of mild maculopapular cutaneous eruptions due to the thiocyanates. Gager⁵ reported 2 cases,

Studies and contributions from the Department of Internal Medicine, service of Dr. Cyrus C. Sturgis, and the Department of Dermatology and Syphilology, service of Dr. Udo J. Wile, University of Michigan Medical School.

1 Pauli, W. Ueber Ionenwirkungen und ihre therapeutische Verwendung, *München med. Wchnschr.* **50** 153-157 (Jan 27) 1903.

2 Westphal, K. Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes. I. Die paradoxe Gefassreaktion auf Abschnürung bei arterieller Hochdruck, *Ztschr. f. klin. Med.* **101** 545-557, 1925.

3 Goldring, W., and Chasis, H. Thiocyanate Therapy in Hypertension. I. Observations on Its Toxic Effects, *Arch. Int. Med.* **49** 321-329 (Feb.) 1932.

4 Takacs, L. Versuche mit Rhodansalzen. I. Einfluss des Rhodan auf Magensekretion, weisse Blutkörperchen, Pulsschlag und Blutdruck, *Ztschr. f. d. ges. exper. Med.* **50** 432-439, 1926.

5 Gager, L. T. The Incidence and Management of Hypertension, with a Note on Sulfocyanate Therapy, *J. A. M. A.* **90** 82-86 (Jan 14) 1928.

Goldring and Chasis³ noted a case and Boig⁶ also mentioned 1. In 1937 Baker and Brunsting⁷ stated that they had observed several cases of these mild cutaneous reactions. Barker⁸ stated that in ten years' experience with this group of drugs, he had observed no severe cutaneous reactions but had noted several cases of mild dermatitis.

Thiocyanates have been used at the University of Michigan Hospital for about three years in selected cases of essential hypertension. During this time a mild, nondescript, erythematous dermatitis has been observed in 4 or 5 patients receiving the drug. These patients have not presented other toxic symptoms, and the eruptions have promptly subsided on discontinuance of the drug.

Regarding the more severe cutaneous reactions, reports of only 5 cases are found in the literature. Logefeil⁹ reported 2 cases, in which a dry, scaly, pruritic dermatitis developed on the entire body, associated with fever and moderate prostration. In 1929 Weis and Ruedemann¹⁰ described a generalized erythematous dermatitis which appeared on the tenth day of administration, 27 Gm having been ingested. The eruption reached its height in four days and became exfoliative. Later, small doses of thiocyanate were again given, and a similar eruption developed. Ayman¹¹ observed a case of generalized maculopapular dermatitis which developed on the eighth day of medication, after 48 Gm of potassium thiocyanate had been taken. The eruption was associated with weakness, abdominal cramps and a temperature of 99.5 F. In 1937 Baker and Brunsting⁷ reported a case of severe dermatitis. This acute generalized papulourticarial eruption was associated with conjunctivitis, pharyngitis, elevation of the temperature and lowering of the blood pressure. No concomitant blood cyanate determinations were reported in any of these cases.

6 Borg, J. F. Experiences in the Use of the Sulfocyanates, *Minnesota Med* **13** 293-296 (May) 1930.

7 Baker, T. W., and Brunsting, L. A. Dermatitis Medicamentosa Resulting from the Administration of Sulfocyanates in the Treatment of Hypertension, *J. A. M. A* **108** 549-550 (Feb. 13) 1937.

8 Barker, M. H. Personal communication to the authors.

9 Logefeil, R. C. Observations on the Use of Potassium Sulfocyanate (Rhodan) in the Treatment of Essential Hypertension, *Minnesota Med* **12** 151-159 (March) 1929.

10 Weis, C. R., and Ruedemann, R. Exfoliative Dermatitis from Potassium Sulphocyanate Therapy, *J. A. M. A* **93** 988 (Sept. 28) 1929.

11 Ayman, D. Exfoliative Dermatitis from Potassium Thiocyanate, *J. A. M. A* **93** 1671 (Nov. 23) 1929.

Recently Barker¹² developed a practical method of performing blood thiocyanate determinations by modifying Schreiber's¹³ technic. He observed that the optimum therapeutic level is 8 to 12 mg per hundred cubic centimeters of blood and that significant toxicity begins to appear at levels of 15 to 30 mg. He noticed that the amount of drug necessary to produce a given level in the blood varies widely in different individuals but that if the blood concentration is studied the dosage can usually be regulated so as to reduce the blood pressure without producing toxic symptoms.

The case which we wish to present is of special interest because, first, the dermatitis was of the unusual severe urticarial type associated with marked constitutional symptoms, second, the eruption developed while the patient was in the hospital, so that daily observations and study were possible throughout the course of the reaction, and, third, blood thiocyanate determinations were obtained.

REPORT OF CASE

C W., a physician aged 41, entered the hospital on July 18, 1938. He was known to have had hypertension for five years, and since January 1937 his blood pressure had averaged 200 to 210 systolic and 120 to 130 diastolic. In May 1938 he noticed blurring of vision in the right eye. He gave a history of urticaria in childhood, attacks of migraine in early adult life and also symptoms of peptic ulcer, which were controlled by a dietary regimen. He stated that both he and his father were "sensitive" to acetylsalicylic acid.

Physical examination revealed a well developed, moderately overweight, middle-aged man. Ophthalmoscopic examination showed slight edema of both disks and many small discrete areas of exudation. The right fundus presented evidence of inactive central chorioretinitis. The retinal vessels were spastic but not sclerotic. Examination of the heart showed the apex beat to be 12.5 cm to the left of the midsternal line in the fourth intercostal space. The heart sounds were of good quality. An occasional extrasystole was present, and the aortic second sound was accentuated. A gallop rhythm was noted at the apex. The blood pressure was 230 systolic and 160 diastolic. The pulmonary fields were clear. The edge of the liver was just palpable on deep inspiration. There was no edema. The pupillary and tendon reflexes were physiologic.

Electrocardiographic study showed definite left axis deviation, with an inverted T wave in all leads, together with notching and slurring of the QRS complex. The heart was of borderline size by orthodiagraphic and teleroentgenographic measurements.

Urinalysis showed a one plus reaction for albumin and one or two finely granular casts per low power field. A urea clearance test showed 80 per cent of normal clearance for the first hour specimen and 71 per cent for the second.

12 Barker, M. H. The Blood Cyanates in the Treatment of Hypertension, *J. A. M. A.* **106** 762-767 (March 7) 1936.

13 Schreiber, H. Ueber den Rhodangehalt in menschlichen Blutserum, *Biochem. Ztschr.* **163** 241-251, 1925.

hour The urine was concentrated to a specific gravity of 1.021, according to the Newburgh-Lashmet concentration test¹⁴

The nonprotein nitrogen content of the blood was 33.5 mg per hundred cubic centimeters. The Kahn test of the blood gave a negative reaction. The hemoglobin value was 95 per cent (Sahli), and the red blood cell count was 5,200,000 per cubic millimeter. The total white blood cell count was 6,650 per cubic millimeter, with a differential count showing 71 per cent neutrophils, 3 per cent eosinophils, 13 per cent lymphocytes and 5 per cent monocytes.

The diagnosis was essential hypertension and hypertensive heart disease, with hypertensive neuroretinitis and right inactive chorioretinitis.

A period of medical management was advised. The patient was placed at rest in bed and given 0.032 Gm of phenobarbital four times daily. On July 22

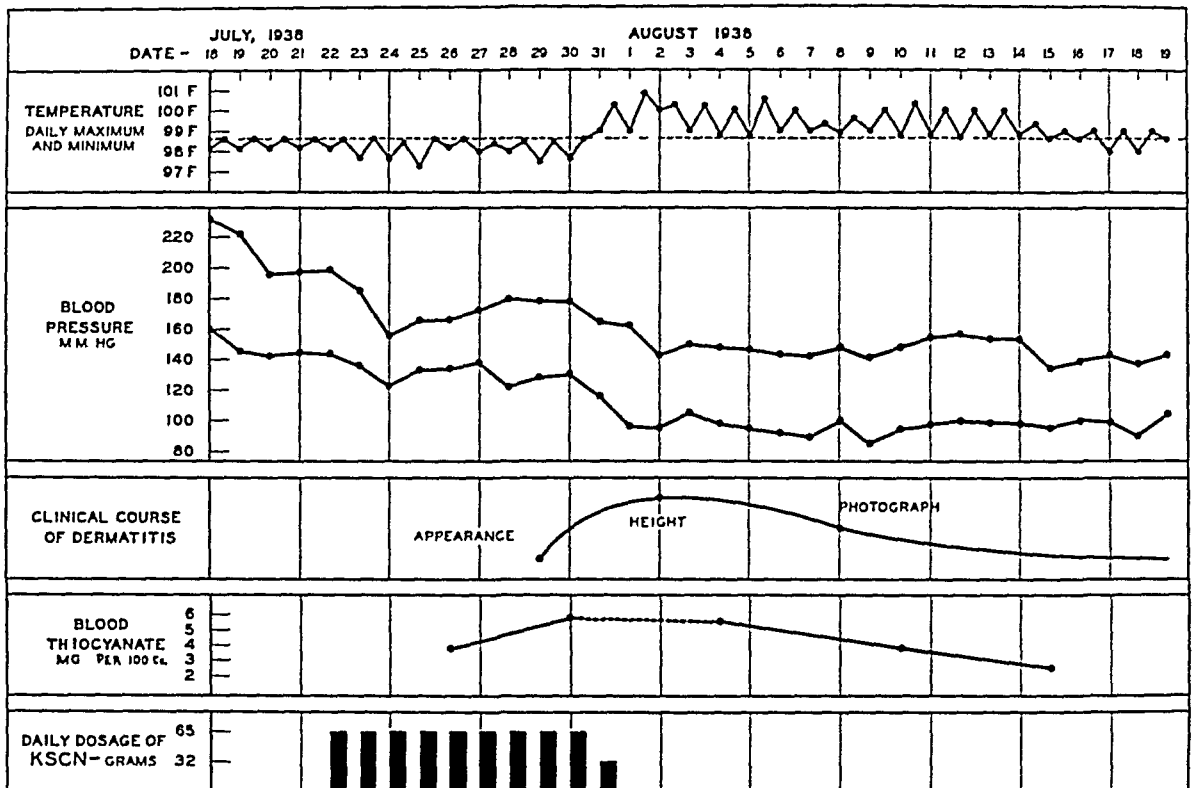


Fig. 1—Correlation of the clinical course of the reaction with the concentration of thiocyanate in the blood

thiocyanate therapy was instituted. This consisted of 0.32 Gm of potassium thiocyanate given in a peppermint water vehicle twice daily. The blood pressure had been 196 systolic and 144 diastolic for four days when the thiocyanate treatment was started. On July 26 the blood pressure was 160 systolic and 130 diastolic. The patient had then received only 2.6 Gm of potassium thiocyanate, and the cyanate concentration of the blood was 3.7 mg per hundred cubic centimeters.

On the morning of July 29, the eighth day of thiocyanate therapy, after 4.55 Gm of the drug had been ingested, a pruritic eruption of the skin appeared. It was

14 Lashmet, F. H., and Newburgh, L. H. An Improved Concentration Test of Renal Function, *J. A. M. A.* 99:1396-1398 (Oct. 22) 1932.

confined to the posterior aspect of the body and consisted of numerous small erythematous maculopapules arranged in groups over the upper part of the arms and back, together with many small erythematous follicular papules over the buttocks and thighs. The following morning, July 30, the blood thiocyanate concentration was 5.7 mg per hundred cubic centimeters. By afternoon the eruption had become much more severe and extensive. Large urticarial wheals appeared

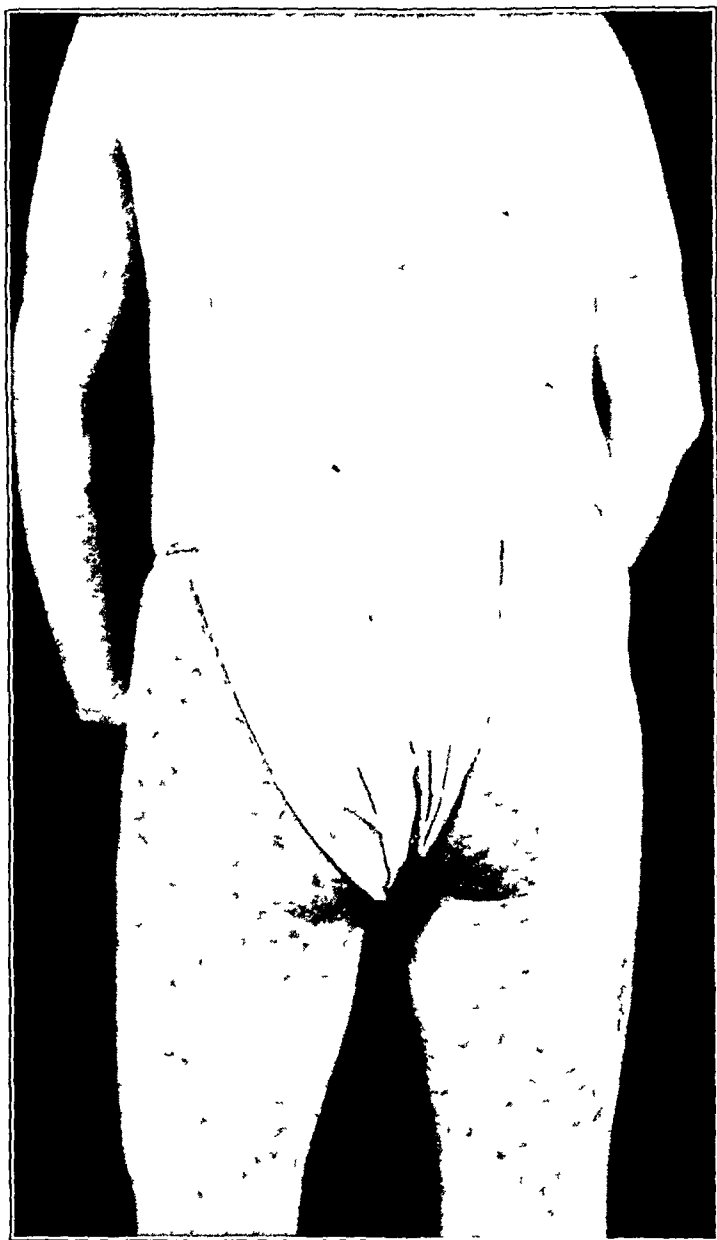


Fig. 2—Thiocyanate dermatitis, the appearance on the eighth day of the eruption

over the trunk, arms and lower part of the legs. The buttocks and thighs were covered with a brightly erythematous maculopapular exanthem. The cutaneous lesions were intensely pruritic and remained so throughout their course. The temperature was 100.2 F, and the conjunctivas were injected. Treatment with both phenobarbital and thiocyanate was discontinued, the patient having received a total of 6.17 Gm. of the latter.

The cutaneous lesions became still more severe, reaching their height on the fourth day after their appearance. The face was markedly flushed, the eyelids were edematous and conjunctivitis with lacrimation was present. There was some obstruction to breathing, due to nasal congestion. The patient complained of sore throat, became hoarse and had an irritative cough productive of small amounts of clear mucoid sputum. Examination of the nose and throat showed the mucous membrane to be pale and edematous. There was a feeling of tightness in the chest, with occasional bilateral pleuritic pain. Asthmatic attacks occurred several times. Anorexia was present together with annoying dysphagia. Burning on urination, headaches and generalized muscular aches added to the patient's discomfort. He was extremely weak. The systemic symptoms persisted throughout the course of the illness. The temperature was elevated to 99.2 to 100.8 F daily until the eighteenth day of the eruption. The blood pressure dropped and remained at an average level of 150 systolic and 110 diastolic. The thiocyanate concentration of the blood fell slowly. A correlation of the clinical course of the reaction and the blood cyanate concentration is represented in figure 1.

The large urticarial lesions persisted for about a week. They then gradually became less erythematous, and their infiltration subsided. The appearance of the patient on the eighth day of the eruption is shown in the accompanying photograph (fig. 2). A rather pronounced, dull erythema persisted for a considerable time, similar to that seen in a fixed eruption. Exfoliation occurred after about two weeks. This was generalized over the body but consisted simply of shedding of the superficial epithelium over the individual lesions. Pigmentation and scaling were still present after three weeks. The patient's strength returned slowly, and he was still weak at the time of discharge, on August 19.

The patient was treated with bland lotions and cool spongings. The taking of fluids was encouraged. Nose drops containing ephedrine sulfate relieved the nasal congestion, and epinephrine hydrochloride given hypodermically controlled the asthmatic attacks. Codeine phosphate seemed to increase the pruritus. On August 8 the use of phenobarbital was resumed (0.032 Gm. four times daily) and was continued until the time of discharge without incident.

Repeated urinalyses revealed essentially the same findings as at the time of admission. A few granular casts persisted, but no hematuria occurred. On August 2, the fifth day of the eruption, the white blood cell count was 10,000 per cubic millimeter, and the differential count showed only 4 per cent eosinophils. However, on August 13, when the eruption was subsiding, the total white blood cell count was 11,700, with 46 per cent neutrophils, 18 per cent lymphocytes, 3 per cent monocytes and 32 per cent eosinophils.

COMMENT

We believe that there is no reasonable doubt that in this case the eruption was produced by thiocyanate. It did not resemble the usual type of phenobarbital dermatitis, and the patient later resumed the use of that drug, with no recurrence of the eruption.

The symptoms associated with this severe cutaneous reaction suggested that a generalized enanthem also occurred. As the reaction occurred at a blood concentration of thiocyanate well below that at which toxic symptoms occur in the average person, we are inclined to consider that the entire reaction was due to idiosyncrasy to the drug.

The patient's history, the urticarial character of the lesions, the pale edematous appearance of the nasal mucous membrane and the marked eosinophilia which developed are other points which indicate that the reaction was allergic in nature

We wish to point out that a satisfactory fall in blood pressure occurred on the fifth day of thiocyanate therapy, when the concentration of thiocyanate in the blood was only 37 mg per hundred cubic centimeters. This was an unusual effect with a blood level as low as that, and we believe that it indicated hypersensitivity of the vascular system also to the drug. If this unusual early drop in blood pressure had been interpreted as a danger signal, the severe reaction which followed might have been averted. This emphasizes the importance of careful daily determinations of the blood pressure as well as simultaneous studies of the thiocyanate level of the blood of patients receiving thiocyanate.

This case also emphasizes the point that thiocyanate should be given with caution to patients with a history of allergy and that its use should be discontinued immediately on the first appearance of any erythematous maculopapular eruption.

SUMMARY

A case of the severe urticarial type of dermatitis medicamentosa due to potassium thiocyanate has been presented. The clinical course of the reaction has been correlated with blood thiocyanate determinations. There was evidence which indicated that the reaction was allergic in nature and that the entire vascular system was involved.

LIPOID PNEUMONIA

REPORT OF TWO CASES

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Pneumonia due to the aspiration of oily preparations into the lungs was first described by Laughlen¹ in 1925. Subsequently other reports have appeared, so that in 1936 Ikeda² was able to collect 24 references to this condition.

Lipoid pneumonia usually occurs in debilitated infants or children, although its occurrence in adults has been described. In the majority of instances the patient suffers from some condition which makes occasional aspiration of materials from the pharynx practically inevitable. The substances which cause the trouble most frequently are nose drops and laxatives containing petrolatum. Cod liver oil, milk, and cream are responsible occasionally.

Lipoid pneumonia occurring in infants or children is referred to as the infantile type of the disease. In adults the pneumonia sometimes develops slowly over a period of years and forms a localized dense fibrous area. This is known as lipoid pneumonia of the adult type. In the majority of the cases, however, lipoid pneumonia in adults is of the infantile type.

Clinically, patients with lipoid pneumonia show the signs and symptoms of low grade pneumonia, with periodic exacerbations due to secondary infection. In cases of the adult type in which the pneumonia develops slowly to form a well circumscribed fibrotic area the disease may imitate chronic granulomatous pneumonia or tumor.

Roentgen examination shows areas of increased density, which in cases of extensive involvement show a tendency to affect both lungs, the right lung predominantly in the lower third of the upper lobe and the apex of the lower lobe, and the left lung in the middle third of the upper lobe and the apex of the lower lobe.³ In cases of chronic involvement

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1 Laughlen, G F. Studies on Pneumonia Following Nasopharyngeal Injections of Oil, *Am J Path* **1** 407, 1925.

2 Ikeda, K. Lipoid Pneumonia of the Adult Type (Paraffinoma of the Lung). Report of Five Cases, *Arch Path* **23** 470 (April) 1937.

3 Reichle, H S. Bronchiogenic Distribution of Fluid and Particulate Matter. Its Site of Predilection and Mechanism of Transfer, *Arch Path* **25** 811 (June) 1938.

in adults the differentiation roentgenologically of this condition from neoplasm or unresolved pneumonia may be difficult

At autopsy the lungs in the infantile type of lipid pneumonia show evidence of reaction of the tissues to a foreign body plus the results of secondary invasion of bacteria. Grossly the consolidated lung tissue is a peculiar grayish yellow, and a cloudy, milky fluid containing minute oily droplets can be expressed from it. Microscopically the alveoli are filled with macrophages containing lipoids. Giant cells, more or less vacuolated, and lymphocytes are present. The septums show edema, fibrosis, infiltration by lymphocytes and spaces filled with lipoids. The adult type is considered to be fundamentally the same as the infantile type except that it is a late stage, being localized and densely fibrous.

The prognosis of the condition is usually poor, more because of the associated disease than because of the lipid pneumonia itself.

Most of the patients with lipid pneumonia encountered at the Cleveland City Hospital have been infants. In the past six months, however, 2 cases of lipid pneumonia in adults have been observed clinically and at autopsy.

REPORT OF CASES

CASE 1—H. K., a white woman aged 73, who entered the Cleveland City Hospital Oct. 18, 1938, had been in good health until September 15, since which time she had had a cough productive of small amounts of greenish white sputum. Dyspnea and a feeling of tightness in the chest were also present. The patient had allowed only salve to "trickle down her throat," but she had not improved. A film of the chest taken October 13 showed moderately dense, coarse streaky mottling in the lower medial portion of the right lung field. This was interpreted as being due to a pneumonic process. The course subsequently was unfavorable, and the patient entered the hospital five days later.

Examination showed her to be dyspneic, cyanotic and acutely ill. There was evidence of severe chronic pulmonary emphysema. Coarse, raucous rales and wheezes were heard over both lungs. The temperature rose from 37 to 40 C (98.6 to 104 F), pulmonary edema developed, and the patient died in thirty-six hours.

Autopsy was done three hours after death. The lungs showed marked emphysema and chronic bronchitis. In the middle lobe of the right lung, near the hilus, there was an area of infiltration measuring 6.5 by 6.5 by 5 cm. This was sharply demarcated, granular and of a peculiar grayish yellow. The pulmonary lymph nodes were normal.

Microscopic examination of the area of consolidation showed numerous large vacuolated mononuclear cells in the alveoli and to a lesser degree in the septums. A few giant cells were present. Interspersed through the area were collections of lymphocytes and polymorphonuclear cells. The alveolar walls were thickened. The scarlet red stain showed fat in the vacuolated cells. In addition, there was some fat free in the alveoli and septums.

The only other important pathologic observations were acute pneumococcal ethmoiditis and sphenoidal sinusitis.

CASE 2—G. C., a white man aged 66, who entered the Cleveland City Hospital Nov. 10, 1938, had a carcinoma of the esophagus. A Janeway gastrostomy was

done on November 25, and the patient had an uneventful convalescence, oral feedings being resumed on the second postoperative day. Roentgen therapy was started December 20, a daily dose of 300 r being administered to both sides of the chest wall anteriorly and posteriorly. The patient's general condition at this time was good. He had moderate difficulty in swallowing, but oral feeding still seemed feasible. His food consisted of a soft diet, with liberal amounts of milk and cream, and he received in addition 30 cc of an emulsion of liquid petrolatum and agar (plain petrolagar) twice a day and 4 cc of cod liver oil three times a day.

On Jan 1, 1939, fever and symptoms referable to the respiratory system appeared. On January 5 a fluoroscopic and roentgen study of the chest showed streaked mottling extending outward from the hilus of the left lung. It was thought that the patient had bronchopneumonia and probably mediastinitis.

Subsequently the patient was weak and lethargic and coughed considerably. The temperature varied between 38 and 39.5 C (100.4 to 103.1 F). Roentgen therapy was discontinued January 23, a total of 2,100 r having been given to each of the four portals. The patient's condition, however, remained unchanged.

On the morning of February 2 his condition, although poor, was virtually as it had been for the previous month except that he was expectorating small amounts of dark blood. Two hours later a large amount of blood suddenly welled out of his mouth and nose, and he died almost at once.

Postmortem examination, done seven hours after death, showed a tumor involving the esophagus at the level of the bifurcation of the trachea. The tumor had eroded into the aorta, there being a fistula between the esophagus and the aorta. There were large amounts of blood in the trachea, the stomach and the upper part of the small intestine.

The upper half of the lower lobe of the left lung was consolidated. The cut surface was smooth, firm and pale yellowish gray. The remaining portions of the lungs showed no significant abnormalities. There was no fistula between the esophagus and the trachea or bronchi. The pulmonary lymph nodes were normal.

Microscopic examination of the area of pneumonia in the upper portion of the lower lobe of the left lung showed the lung to be practically airless. The alveoli contained many vacuolated phagocytic cells in addition to moderate numbers of lymphocytes and polymorphonuclear cells. A few vacuolated multinucleated foreign body giant cells were present. In a few areas there was early organization of the exudate. The alveolar walls were thickened and in some areas contained fibroblasts in addition to cells similar to those found in the alveoli.

The scarlet red stain showed large amounts of free and phagocytosed fat in the alveoli and interstitial tissue.

COMMENT

In cases of lipid pneumonia oil usually enters the lungs because of some serious disease which makes aspiration of material from the pharynx practically unavoidable. In case 1, however, there was no such explanation, oil having entered the lungs because of the patient's habit of intentionally letting oily salve trickle down her throat. The hazard of such a procedure is shown by the fact that the clinical course and pathologic observations indicate that the lipid pneumonia was an important factor in the patient's death.

The lipid pneumonia in this case was of the infantile type, and from the clinical standpoint it is known that the pneumonia must have

been of recent origin, because the use of oil did not extend over a period of more than one month before death occurred. That early lipoid pneumonia in the adult is indistinguishable from the infantile type has been emphasized by Ikeda.² The area of pneumonia becomes fibrotic and localized to form a tumor-like mass only with the passage of time. In this case, however, the patient died before such changes could occur.

The second case is less unusual in regard to the manner in which oil entered the lungs. It seems probable that dysphagia incident to the carcinoma of the esophagus resulted in aspiration into the lungs of material intended to pass down the esophagus. The material no doubt entered the lungs by way of the larynx, because autopsy revealed no fistula between the esophagus and the trachea or bronchi. The exact etiologic agent in this case is not clear, since the patient received several oily substances which might have been responsible. The exposure lasted about two months, and from a pathologic standpoint the case affords further evidence that lipoid pneumonia in its early stages in the adult is fundamentally the same as the infantile type. The early organization of the exudate indicates, however, that the pneumonia in this case was approaching an intermediate stage between the infantile and the adult type.

SUMMARY

Two cases of lipoid pneumonia in adults indicate the hazard of introduction of oily materials into the pharynx under conditions in which aspiration of the material may occur. In 1 instance oil entered the lungs owing to the patient's habit of letting oily salve trickle down her throat, and in the other case oil entered the lungs as a result of dysphagia due to esophageal obstruction. The cases also illustrate that the early stages of lipoid pneumonia in the adult are indistinguishable pathologically from the infantile type of the disease.

Progress in Internal Medicine

VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE, WITH A
CRITICAL REVIEW OF THE SURGICAL TREATMENT

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GÉZA DE TAKÁTS, M D

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AND

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CHICAGO

A REVIEW OF SOME OF THE RECENT LITERATURE

By DR SCUPHAM AND DR VAN DELLEN

Many reports of academic and practical value have been published during the past year. We have endeavored, as far as possible, to include for consideration only those articles which contributed new information or those which seemed of importance because they supplemented or confirmed present beliefs. An attempt was also made to evaluate certain controversial data reported on related subjects by various authors. Considerable space has been devoted to hypertension because of the increasing interest in it shown by the numerous contributions on this subject.

PHYSIOLOGY

Grant and Holling¹ made additional studies on the differences between the vascular responses of the proximal and the distal parts of the human limbs. Recent observations have revealed that while warming of the body provokes a large increase in blood flow and cutaneous temperature in the hands and feet, it causes no more than a slight rise in blood flow and cutaneous temperature in the proximal parts of the extremities. Neither flushing nor warming of the skin of the proximal portion occurs if the circulation to the extremity has been arrested.

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1 Grant, R. T., and Holling, H. E. Further Observations of the Vascular Responses of the Human Limb to Body Warming. Evidence for Sympathetic Vasodilator Nerves in the Normal Subject, *Clin. Sc.* 3: 273, 1938.

This variation has been explained as being due to the differences in the distribution of the arteriovenous anastomoses. The persons tested were subjected to strong warming of the body, accomplished by immersing two or three extremities in water maintained at 45 to 46 C with all portions of the body completely covered except the face and the limb under observation. Blood flow and cutaneous temperature were measured by methods previously described. It was found that when warming of the body was pushed to excess in this manner vasodilatation developed in the proximal areas of the extremities. Observations were made on several patients before and after sympathetic ganglionectomy and on several subjects following nerve block. Following surgical operations the blood flow was increased but soon diminished so that it returned almost to the preoperative level within a week. Strongly warming the body at this time failed to provoke the vasodilatation observed before operation. Similar responses were noted over the anesthetized skin of the arm and leg after nerve block. The authors expressed the opinion that these observations demonstrated that the vasodilatation provoked in the arm and leg by heating the body was dependent on the integrity of the sympathetic nerves, as was already demonstrated for the hand and foot. The results obtained from these and previous observations were interpreted as indicating two means of defense against rise in body temperature. The first is brought into action by relatively gentle heating and consists chiefly of dilatation of the arteriovenous anastomoses in the extremities through inhibition of vasoconstrictor tone. The second occurs when the heating is more intense and consists mainly in general dilatation of the cutaneous vessels associated with sweating. The vasodilatation produced in the proximal part of the extremity was brought about by stimulation of cutaneous sympathetic nerves.

Fatheree and Allen,² while investigating the mechanism of indirect vasodilatation, corroborated the existing views on this subject. They demonstrated that indirect vasodilatation induced by warming an extremity depended on the return of blood from the warmed extremity to the general circulation. In addition it was shown that the occurrence of indirect vasodilatation in a digit depended on the integrity of its sympathetic nerve supply. They were able to present evidence demonstrating the presence of vasodilator nerves in the lower extremities in 2 cases of Raynaud's disease. Keeping the feet in a cool environment, they showed that a regional nerve block of the lower extremity prevented induction of indirect vasodilatation by heat in the anesthetized

2 Fatheree, T J, and Allen, E V. Sympathetic Vasodilator Fibers in the Upper and Lower Extremities. Observations Concerning the Mechanism of Indirect Vasodilation Induced by Heat, *Arch Int Med* 62 1015 (Dec.) 1938

areas while vasodilatation was occurring in the unanesthetized areas of the same foot. They were unable to demonstrate the presence of sympathetic vasodilator fibers in normal persons by this method.

Atlas³ studied the cutaneous temperature of a patient who had a complete traumatic division of the peripheral nerves to the left arm. He noted that the response in cutaneous temperature was similar to that seen after cervicothoracic sympathetic ganglionectomy when the postganglionic fibers were sectioned. He was able to demonstrate the phenomenon of increased sensitivity of the blood vessels to epinephrine as a cause of vasoconstriction. He suggested this as the possible explanation of the vasomotor and nutritional changes in denervated tissue. Grant and Holling,¹ in a study of a similar case, in which the right external popliteal nerve was accidentally severed, were unable to induce indirect vasodilatation in the extremity in a cool environment. The best explanation for this phenomenon was thought to be furnished by the destruction of the vasodilator fibers. There is an increasing tendency to regard this explanation as correct.

Wells, Youmans and Miller⁴ measured pressure in the muscle as well as in the superficial tissue. They confined their studies chiefly to observations on normal subjects. The tissues of the leg were chosen because of the failure of edema to develop in the legs of normal persons on prolonged quiet standing. They noted that the pressure in the leg muscles which were tightly covered with fascia rose to 50 cm. of water or higher during prolonged venous congestion. They expressed the belief that pressures of this magnitude probably were sufficient to stop filtration into these muscles during quiet standing. In muscles loosely covered, such as the gastrocnemius, the pressure did not rise above 20 cm. of water during congestion. They showed that the intramuscular pressure was affected independently by several factors, of which the most important were the lightness of the fascia, the amount of intravascular and extravascular fluid present and the components of contractile force of the muscle. Maximal voluntary contractions of various muscles elevated intramuscular pressure to values ranging from 10 to 118 cm. of water. As such pressures in most muscles are lower than the level of diastolic arterial pressure, blood flow through these muscles cannot be stopped during ordinary contractions. The leg volume continued to increase indefinitely during quiet standing. In each case the ratio of the final

3 Atlas, L. N. The Etiology of Vasomotor and Nutritional Changes Following Peripheral Nerve Section, *Surgery* 4:718, 1938.

4 Wells, H. S., Youmans, J. B., and Miller, D. G., Jr. Tissue Pressure (Intracutaneous, Subcutaneous, and Intramuscular) as Related to Venous Pressure, Capillary Filtration, and Other Factors, *J. Clin. Investigation* 17:489, (July) 1938.

rate of filtration to the initial rate was of the magnitude to be expected on the assumption that filtration ceases in muscles under high pressure but continues indefinitely in the skin and gastrocnemius, the low pressure filtering areas. They did not assume that fluid left the leg through lymphatics during quiet standing.

Sodeman and Burch⁵ described a simple and accurate method for measuring the distensibility of skin. Horizontal stretching of the skin of a limb after the limb has been placed in a standard position is easily accomplished with a small caliper of known calibration. The normal mean values for the pretibial area, the dorsum of the foot, the midline of the abdomen below the umbilicus, the volar surface of the forearm and the dorsum of the hand were found to be 0.31, 0.59, 2.07, 0.93 and 1.34 mm per cubic millimeter per hundred grams, respectively. The regional variations disclosed less distensible skin in the lower extremities.

Edema, certain vascular diseases and some dermatoses were found to produce changes in the normal distensibility of the skin. As edema progresses the distensibility decreases, and with recession of the edema the distensibility tends to return to a normal range. The loss of distensibility was found to be an important factor in limiting the formation of edema. In urticaria, senile atrophy, occupational atrophy, allergic eczema and scleroderma, definite changes in the distensibility of skin were observed which correlated with the clinical state of the patient.

Blood Flow—The rate of blood flow in the normal finger was studied by Wilkins, Doupe and Newman⁶. The method of Hewlett and Van Zwaluwennburg was adapted, and measurements were made on a small plethysmograph carefully fitted to the last two phalanges of the finger. The rate of blood flow to the finger was found to range from 0.02 cc per minute per 10 cc when the peripheral vessels were constricted to 12 cc when they were dilated. These figures showed that the blood flow to the normal finger may be increased as much as a hundred times during vasodilatation induced by warming of the body. When the vessels are already dilated, the flow may be temporarily decreased as much as twenty times following a vasoconstricting stimulus. They demonstrated also that the increase in blood flow resulting from local heating of the finger was not as great as that produced by warming of the body. The blood flow to the terminal phalanx was found to be greater than that to the middle phalanx of the finger when the vessels were dilated.

5 Sodeman, W. A., and Burch, G. E. A Direct Method for the Estimation of Skin Distensibility with Its Application to the Study of Vascular States, *J. Clin. Investigation* **17** 785 (Nov.) 1938.

6 Wilkins, R. W., Doupe, J., and Newman, H. W. The Rate of Blood Flow in Normal Fingers, *Clin. Sc.* **3** 403 (Dec.) 1938.

Stead and Kunkel⁷ described a plethysmographic method for measuring quantitatively the blood flow in the foot. With a standard correction for the inertia of the plethysmograph and a bellows system, the instrumental error was found to be 3 per cent. Using this plethysmograph, they⁸ studied the blood flow in the normal foot. The flow was recorded as the cubic centimeters of blood per minute per hundred cubic centimeters of tissue. Studies were made at 43 C., and the flow at this temperature was designated as the maximal flow. The average maximal flow in thirty-four normal persons was 17.1 cc., with the highest 25.9 cc. and the lowest 11.1 cc. The values were lower for males than for females, the averages being 16.3 cc. for the former and 18.7 cc. for the latter. In the presence of a normal cardiovascular system the blood flow showed no appreciable decrease with age. The average difference between the maximal flow in the right and that in the left foot was 1.8 cc. Simultaneous readings on one hand and one foot revealed the average flow of the hand to be 32 cc. and that of the foot 15.7 cc. These measurements are indicative of the considerably smaller reserve of blood in the foot as compared with that in the hand.

In arteriosclerosis and thromboangitis obliterans the maximal blood flow to the foot was reduced 50 per cent without symptoms or trophic disturbances. When the flow was reduced to one-third the normal value, or to the level of 5 cc. or below, symptoms or trophic disturbances usually were present. In both arteriosclerosis and thromboangitis obliterans severe intermittent claudication in the calf was in some patients incapacitating, though the blood flow in the foot was as great as in many normal persons. Thus the presence of an adequate supply of blood to the foot did not eliminate the possibility of obliterative disease involving the vessels of the calf muscles. This is in keeping with observations reported last year.

Continuing their studies with the plethysmograph, Kunkel, Stead and Weiss⁹ compared the blood flow and vasomotor reactions of the hand and foot with those of the forearm and calf. This seemed necessary because of the wide variations in the proportion of muscle to skin in these parts and because of the presence of numerous arteriovenous anastomoses in the skin of the hands and feet. Following strong

7 Stead, E. A., and Kunkel, P. A Plethysmographic Method for the Quantitative Measurement of the Blood Flow in the Foot, *J. Clin. Investigation* **17** 711, 1938.

8 Kunkel, P., and Stead, E. A. Blood Flow and Vasomotor Reactions in the Foot in Health, in Arteriosclerosis and in Thromboangitis Obliterans, *J. Clin. Investigation* **17** 715, 1938.

9 Kunkel, P., Stead, E. A., and Weiss, S. Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli, *J. Clin. Investigation* **18** 225 (March) 1939.

sensory stimulation, the forearm and calf responded in three ways (1) by a decrease in volume after a latent period of from three to nine seconds, (2) by an increase in volume after a latent period not exceeding two seconds and (3) by a biphasic response—first an increase in volume with a short latent period, usually not exceeding two seconds, and subsequently a decrease in volume. The authors were of the opinion that an active reflex vasoconstriction took place in cases in which a decrease in volume occurred. In cases in which an increase in volume occurred it was believed to be the result of a transient increase in cardiac output and a passive distention of the vascular bed. Numerous variations in response were noted not only in different persons but also in the same persons. The vessels in the upper extremities were more sensitive than those in the lower. Constrictor responses of the forearm and calf paralleled the vasoconstrictor reactions which have been shown to occur in the hand and foot following similar sensory stimulation. The intensity of the reactions had to be greater to produce vasomotor responses in the forearm and calf as compared with the hand and foot. The blood flow was greater in the hand and foot than in the forearm and calf when induced by local heat of 43 C. Local heat of the same degree produced complete vasodilatation in the skin but relatively slight dilatation in the underlying muscles, whereas exercise had the opposite effect, producing dilatation in the muscles but not in the skin. The latter observation was not influenced by variations in external temperature. Epinephrine, 1 cc of a 1:1,000 solution injected subcutaneously, caused a marked decrease in blood flow in the hand and foot and a moderate increase in blood flow in the forearm and calf. Pitressin (betahypophamine), 1 cc injected intramuscularly, caused a decrease in flow in the hand and foot, as did epinephrine. It also caused a moderate decrease in flow in the forearm and calf. Neither of these drugs interfered with the dilatation of the vessels in the muscles in response to exercise or induced arterial occlusion.

The standard technic for using the same type of plethysmograph was described in detail by Abramson, Zazeela and Marrus¹⁰. Numerous mechanical and physical difficulties were mentioned, especially those concerned with the position of the lower extremity, the position of the cuff, occlusion pressure, air in the apparatus, calibrations and the diameter of the glass tube of the recording apparatus. In their second article¹¹ various physiologic factors were discussed in relation to the

10 Abramson, D. I., Zazeela, H., and Marrus, J. Plethysmographic Studies of Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, *Am Heart J* **17** 194 (Feb.) 1939.

11 Abramson, D. I., Zazeela, H., and Marrus, J. II. Physiologic Factors Affecting Resting Blood Flow in the Extremities, *Am Heart J* **17** 206 (Feb.) 1939.

blood flow Normal values, somewhat lower than those of Kunkel and Stead, were obtained They found that the hands were more difficult to control than the feet, because they were more easily subjected to spontaneous vasomotor changes In a number of persons they observed a slight drop below the base line in the blood flow of the lower extremities after the release of the occlusive pressure This appeared to have its origin in a local reflex, as it was independent of the amount of pressure used and a paravertebral block failed to abolish it Studies were also made on persons with various bilateral maladies In a patient with increased venous pressure in the right arm, the flow in this arm was found to be definitely increased as compared with that in the other Little difference in blood flow was noticed in the two arms of a person with unilateral hypertension Decreased blood flow was noted in a person during sleep and in another who went into shock following an injection of "spasmalgine," a proprietary preparation containing derivatives of atropine, opium and papaverine

Using a new and sensitive photoelectric recording type of plethysmograph, Martin, Marcellus and Sykowski¹² studied the coincidental synchronous respiratory waves They found them to be of mechanical origin and due essentially to the increase in pressure in the thoracic and abdominal vessels with each respiration They believed that this pressure was transmitted to the extremities They noted that the magnitude of the waves of respiration was dependent on the patency of the arterial bed, decreasing in size with vasoconstriction and increasing with vasodilatation They suggested that changes in this magnitude be studied along with those in pulse rate and pulse volume in the digits This article and others on this subject demonstrate the difficulties and pitfalls of this method of study

The details of the photoelectric plethysmograph devised by Hertzman¹³ were described in last year's review In a recent article Hertzman discussed the numerous sources of error involved in the quantitation of the cutaneous plethysmogram, especially those bearing on the problem of the blood equivalent and on the quantitative accuracy of this device Errors occur through movements of the skin, through the presence of a large artery in the immediate neighborhood of the area observed and through improper contact of the plethysmograph with the skin Readings cannot be obtained over the trunk, as the movement of the skin over this area cannot be controlled The possibility of distant or deeper tissues influencing the recording of the pulse is discussed but is con-

12 Martin, S J, Marcellus, F S, and Sykowski, P Plethysmographic Studies with Special Reference to Waves of Respiration, *J Lab & Clin Med* **24** 111, 1938

13 Hertzman, A B The Blood Supply of Various Skin Areas as Estimated by the Photoelectric Plethysmograph, *Am J Physiol* **124** 328 (Nov) 1938

sidered of little significance. The importance of a constant source of light is stressed. Simultaneous photoelectric and mechanical plethysmograms of the fingers were compared, and the various vascular responses to some of the common procedures were recorded to establish the validity of the photoelectric plethysmograph. The argument was advanced and supported by suitable data that with normal circulatory dynamics and under resting conditions the volume pulse of an area of skin was a measure of the richness of the arterial blood supply of that area. The finger pad was found to have the most abundant arterial supply. Next in order of frequency were the ear lobe, toe pad, palm of the hand, skin of the forehead and face, dorsa of the finger, hand and foot, forearm, knee and tibia. Readings were made during various seasons, and the highest readings were obtained in the summer. Hertzman was unable to demonstrate that the difference in vasomotor reactions in various areas depended solely on richness of arterial supply, as he observed a surprising seasonal constancy in pulse volume in the forehead, nose, forearm and dorsa of the hand and foot in contrast to the dilatation in warm weather in the finger pad, toe pad and ear.

Mendlowitz¹⁴ studied the blood flow in clubbed fingers on patients with diverse pathologic conditions. The maximum heat elimination was used as an index of blood flow. The various responses of the blood vessels to changes in environmental temperatures were found to be within normal limits. In patients with clubbing of the fingers secondary to pulmonary or to congenital cardiac disease the blood flow of the distal phalanges was increased. In the same patients pressure was increased in the digital but decreased in the brachial-digital arteries. In patients with hereditary clubbing these pressures and gradients were normal. In patients with unilateral clubbing the blood flow of the involved finger tips may or may not be increased or decreased. In these patients no significant change was found in blood pressure gradients.

Scull¹⁵ described a new method of visualizing changes in pressure and volume for the study of variations in peripheral circulation. He utilized the phenomenon that a pattern of light and dark bands appears when pressure is applied to an ordinary glass cover slip rigidly fixed to a microscopic slide. This is due to the interference of light waves associated with reflecting surfaces separated by a thin layer of air of nonuniform thickness. When the pressure applied varies, the thickness of air is modified, which in turn alters the interference pattern. He

14 Mendlowitz, M. Some Observations on Clubbed Fingers, *Clin Sc* **3** 387 (Dec) 1938

15 Scull, C. W. A Simple Method for Visualizing Pressure and Volume Changes Applicable to Observations on the Rhythmic Variations in the Peripheral Circulation, *J Lab & Clin Med* **24** 753 (April) 1939

applied this simple apparatus to the radial artery or to the finger, and with each pulsation various movements of the band of light were produced. Obstructing the flow of blood resulted in prompt cessation of the movement of these bands. He suggested that this apparatus be used for purposes served by other oscillometric and sphygmoscopic devices. Considerable refinement appeared to be necessary. The main objection was that a permanent record of data could not be obtained.

Bazett¹⁶ contrasted the effects on blood volume and circulation of high temperatures applied in acute experiments or in treatments of short duration with those of milder temperatures applied chronically for days. In the analysis of the effects of heat it was necessary to distinguish the parts played by (a) local dilatation in the cutaneous vessels, with the accompanying local increase in rate of flow, capillary pressure and fluid transudation, (b) compensatory reduction of the vascular bed in areas other than the skin, which allows dilatation in the cutaneous vessels even when the blood volume is unchanged or reduced, (c) increases in blood volume on exposure to heat, which form an alternative method of compensation in lieu of vasoconstriction, and (d) alterations in cardiac output.

The part played by each of these factors was discussed in detail. Particular attention was given to blood volume and its effect on the cardiovascular system. Experiments with a moderate, steadily maintained rise in environmental temperature, similar to that present during the summer, revealed a significant increase in blood volume, which apparently was an adaptation to the prolonged peripheral vasodilatation produced by exposure to moderate heat over a period of days. The author was doubtful whether changes in blood volume could be produced by fluctuating temperatures.

Temperature of Skin—Opinions appear to vary as to the changes in the cutaneous temperature of the extremities produced by changes in posture. Roth, Williams and Sheard¹⁷ noted an increase in cutaneous temperature when the subjects were in an upright position and a decrease when the legs were elevated. They attributed these alterations in temperature to changes in the peripheral circulation as a result of changes in hydrostatic pressure. Their observations were in keeping with those previously reported by other authors of a decrease in the velocity of blood flow, an increase in the venous pressure and an average increase of about 4 per cent in the volume of the lower extremities as measured by the plethysmograph while the legs were in a dependent position.

16 Bazett, H. C. The Effect of Heat on the Blood Volume and Circulation, J. A. M. A. **111** 1841 (Nov. 12) 1938.

17 Roth, G. M., Williams, M. M. D., and Sheard, C. Changes in Skin Temperatures of the Extremities Produced by Changes in Posture, Am. J. Physiol. **124** 161 (Oct.) 1938.

Mayerson and Toth,¹⁸ on the other hand, noted a decrease in both the surface and the subcutaneous temperatures of subjects who were suddenly changed to an upright position. They attributed this decrease to compensatory vasoconstriction as a normal adjustment to the upper extremities. They expressed the opinion that their findings were in keeping with those of Hill and Barnard, who noted similar vasoconstriction in the splanchnic area. Roth, Williams and Sheard¹⁷ and Mayerson and Toth¹⁸ reported on persons observed under similar basal conditions, using equally sensitive thermocouples. It is difficult to explain their opposite results. Roth, Williams and Sheard had their subjects standing on blankets, clothed in light pajamas and tilted at angles of 15 and 20 degrees (most favorable position for vasodilatation), whereas Mayerson and Toth used nude subjects suspended on a tilting table at angles of more than 60 degrees. In the latter group syncope was not uncommon. In addition, simultaneous subcutaneous temperatures were taken and studies of blood pressure were made. The method used by Mayerson and Toth was certainly more conducive to vasoconstriction. In addition, tilting patients as the latter authors did must certainly influence all of the compensatory mechanisms regulating blood pressure.

Freeman and Nickerson¹⁹ observed the cutaneous and rectal temperatures of normal subjects exposed to different environmental temperatures for two hours—10 subjects were exposed to a temperature of 68 F and an equal number to a temperature of 59 F. At both 59 and 68 F the cutaneous temperatures fell markedly, more rapidly in the first hour and more precipitously at 59 than at 68 F. The fall was the least on the forehead and greatest on the extremities. The rectal temperature showed little change for an hour, but after that it began to fall, more rapidly at 68 than at 59 F. There was a significant individual variation as to the temperature levels. The difference was greatest in the extremities. The rate at which the cutaneous temperature fell was independent of the initial level of the rectal temperature and only slightly influenced by the initial cutaneous temperature. The average levels of cutaneous and rectal temperatures were slightly related to each other but in an opposite direction.

Circulation Time—Mayerson, Sweeney and Toth²⁰ studied the influence of posture on the circulation time. They used the method of

18 Mayerson, H. S., and Toth, L. A. The Influence of Posture on Skin and Subcutaneous Temperatures, *Am J Physiol* **125** 474 (March) 1939.

19 Freeman, H., and Nickerson, R. F. Skin and Body Temperatures of Normal Individuals Under Cold Conditions, *J Nutrition* **15** 597 (June) 1938.

20 Mayerson, H. S., Sweeney, H. M., and Toth, L. A. The Influence of Posture on Circulation Time, *Am J Physiol* **125** 481 (March) 1939.

Spier, Wright and Saylor The solution was injected into the leg veins, and a greatly increased time was noted with the subject in an upright position In some cases readings could not be obtained They came to the conclusion that the slowing was due to stagnation or pooling of the blood in the veins of the extremities

Capillaries —Brewer²¹ was able to demonstrate rhythmic changes in the capillaries of the skin associated with the cyclic menstrual rhythm These changes consisted essentially of changes in capillary fragility He was able to produce capillary hemorrhages with greater ease during the few days prior to and on the first day of menstruation than during the remainder of the cycle He expressed the opinion that these changes were a direct result of vascular spasm and suggested that menstruation was not a local but a generalized vascular phenomenon There is no evidence to date indicating that vasospasm is related to increased capillary fragility

White and Jones²² studied the rate of filtration through the capillary walls in various pathologic and control sites They used a pressure plethysmograph after the methods of Landis and Gibbons, regulating it after the method of Smirk Obstructing venous pressures were used which were greater in each case by a constant amount than the colloid osmotic pressure of the serum The range of readings observed in normal controls was very wide and was not significantly exceeded in any of the pathologic states studied

Leydhecker²³ found little relationship between the capillaries in the nail bed and those of the eyes In only 7 of 31 patients were the findings significant As these 7 patients were over 40 years of age, he was unable to come to any definite conclusions A definite relationship was noted by Gifford and Marquardt in certain vasospastic phenomena Their contribution will be discussed under "Angiospastic Disturbances," page 613

Oscillometry —A new recording oscillometer was described by Friedman, Ott and Oughterson²⁴ It was found suitable for precise measurements of the vascular pulsations in the toes and finger tips

21 Brewer, J I Rhythmic Changes in the Skin Capillaries and Their Relation to Menstruation, *Am J Obst & Gynec* **36** 597 (Oct) 1938

22 White, B, and Jones, C M The Rate of Filtration Through the Capillary Walls as Measured by the Pressure Plethysmograph Observations on Control Subjects and on Patients with Intrahepatic Disease, Thyrotoxicosis and Myxedema, *J Clin Investigation* **18** 73 (Jan) 1939

23 Leydhecker, F K Capillaruntersuchungen am Fingernagelsaum von Augenkranken, *Arch f Ophth* **139** 97, 1938

24 Friedman, I, Ott, L H, and Oughterson, A W A New Sensitive Recording Oscillometer, *Am Heart J* **16** 575 (Nov) 1938

Action of Drugs—Perlow²⁵ studied the effect of prostigmin on the temperatures of the skin in 1 normal man and 2 women with mild vasospastic phenomena. The prostigmin was given in doses of 0.5 mg subcutaneously and in doses of 15 mg by mouth. With both methods of administration a rise in temperature was noted, higher when the drug was given by mouth. The response was not as great as after a peripheral nerve block. A histamine skin test evoked a reaction of increased intensity following administration of prostigmin. These studies indicated to the author that prostigmin produced arterial rather than arteriolar or capillary dilatation.

Littauer and Wright²⁶ were unable to secure as much vasodilatation with papaverine hydrochloride as with the simple procedure of immersion in water for the same purpose. The papaverine hydrochloride was given intravenously in doses of 0.03 Gm ($\frac{1}{2}$ grain) or more. The temperature of the skin was used as an index of vasodilatation. Two normal persons as well as a number with peripheral vascular diseases were studied. Blood pressure readings were taken simultaneously. They were found to be slightly lowered. In a few instances capillary changes were noted with the capillary microscope. Color changes seldom occurred. It is unfortunate that in these studies cutaneous temperature was the sole index of vasodilatation observed. Other methods, such as oscillometry, might have shown evidence of vasodilatation, as these results are not in keeping with other current clinical reports.

Saland²⁷ noted the effect of benzedrine sulfate and cigarettes on a small group of normal persons and patients suffering from occlusive types of vascular diseases. Following ingestion of benzedrine sulfate, a drop in cutaneous temperature was noted along with a rise in blood pressure and a slowing of the pulse. Observations on cutaneous temperature following smoking were found inconstant. Helmer, Kohlstaedt and Page²⁸ isolated nicotine from the urine of persons who smoked. Its pharmacologic properties were the same as those of pure nicotine. They found that most of the nicotine disappeared from the urine within three or four days after smoking was discontinued. Nicotine appeared to be the substance responsible for the marked pressor action of many specimens of urine. They noted that unless tobacco was

25 Perlow, S. Vasodilating Action of Prostigmin, *J Pharmacol & Exper Therap* **66** 66 (May) 1939

26 Littauer, D, and Wright, I. S. Papaverine Hydrochloride. Its Questionable Value as a Vasodilating Agent for Use in the Treatment of Peripheral Vascular Diseases, *Am Heart J* **17** 325 (March) 1939

27 Saland, G. Benzedrine Sulfate and Cigarettes. Effect on Skin Surface Temperature, *New York State J Med* **38** 1462 (Nov 15) 1938

28 Helmer, O. M., Kohlstaedt, K. G., and Page, I. H. Isolation of Nicotine from Human Urine, *Am Heart J* **17**:15 (Jan) 1939

eliminated as a source of pressor substance in urine, conclusions relating urinary pressor substances to arterial disease are not justifiable. It was suggested that nicotine might be retained by the body when there is a decrease in renal function.

Scarborough and Stewart²⁹ were able to reduce the number of hemorrhages in patients with vitamin deficiencies by oral administration of hesperidin (vitamin P). This effect was observed when petechial hemorrhages were induced by application of pressure and in cases in which spontaneous hemorrhages were observed after administration of preparations of arsenic or bismuth. The authors expressed the opinion that the hemorrhagic tendencies in these cases were independent of the presence of ascorbic acid in the diet.

Roome³⁰ studied in dogs the effect of small doses of epinephrine on the blood flow in the femoral artery. The studies were done with a strohmuhr. The most frequent type of response was a combined dilatation and constriction with a variation of these two phases in their time relationship according to the rate of flow. No pure dilator effects were observed. He expressed the belief that the site of dilatation was in the capillaries and that the site of constriction was in the arterioles and arteries.

The vasodilating effect of nicotinic acid was noted by Spies, Bean and Stone³¹ incidental to their study of this drug on pellagra. Following oral or intravenous administration of nicotinic acid, flushing, burning, itching and a sensation of increased local heat in the skin were noted. Definite increases in temperature of the skin of the face, neck and trunk were recorded, with no change or a lowering in the temperature readings for the hands and feet. The similarity of the drug to histamine when given intracutaneously was noted. Acetylcholine was found to be destroyed more rapidly than nicotinic acid, although both gave similar cutaneous responses.

Fellinger and Schweitzer³² reported the clinical histories of 3 patients in whom severe vascular impairments developed in connection with mercury poisoning. It was impossible to make anatomic studies on the vessels of these patients, but the clinical manifestations of the vascular lesions resembled those of the various forms of obliterating endarteritis, however, in their unusually rapid, almost fulminating course they differed from idiopathic vascular diseases.

29 Scarborough, H., and Stewart, C. P. Effect of Hesperidin (Vitamin P) on Capillary Fragility, *Lancet* **2** 610 (Sept 10) 1938.

30 Roome, N. W. The Effects of Intra-Arterial Epinephrin on the Blood Flow in an Extremity, *Am J Physiol* **123** 543 (Sept) 1939.

31 Spies, T. D., Bean, W. B., and Stone, R. E. The Treatment of Sub-clinical and Clinical Pellagra, *J. A. M. A.* **111** 584 (Aug 13) 1938.

32 Fellinger, K., and Schweitzer, F. Vascular Diseases After Poisoning with Mercury, *Arch f Gewerbepath u Gewerbehyg* **9** 269 (Dec) 1938.

Maijala³³ reported the death of a patient following subcutaneous administration of 0.8 mg of histamine. As this patient had syphilitic aortitis with obstruction of the coronary orifices, the author cautions against the use of this drug in patients with this type of disorder.

THROMBOANGIITIS OBLITERANS

Westcott and Wright³⁴ studied the problem of specific hypersensitiveness of the skin to tobacco in 35 cases of thromboangitis obliterans and 36 control cases. In all cases in which marked reactions to tobacco were shown, passive transfer studies were made. They concluded that patients with thromboangitis obliterans did not show a higher incidence of positive cutaneous reactions than the control group, positive reactions being found in 42.8 per cent of the former and 48 per cent of the latter. They expressed the belief that the discrepancies apparent in the reports of various authors were probably due to erroneous interpretation, as the chemical irritation of tobacco may produce many nonspecific reactions. Harkavy,³⁵ on the other hand, found sensitivity to tobacco in 70 per cent of a large series of cases. He studied 12 cases in detail, in 10 of which thromboangitis obliterans was present, in 1 migrating phlebitis and in 1 acute thrombosis. He made biopsies on immediate and delayed skin reactions to injected tobacco and to injected saline solution as a control. Histologic sections of the immediately occurring urticarial wheals showed eosinophils in varying number. In 3 cases in which delayed reactions were noted an acute dermatitis was found. The exciting role of tobacco in the 12 cases studied was, in addition, corroborated clinically by the arrest in the progress of the symptoms following cessation of the use of tobacco.

Boyd³⁶ studied 25 cases of thromboangitis obliterans. He was able to divide this condition clinically into a proximal and a distal type. In the proximal type the initial symptom was intermittent claudication of vessels in the calf muscles with marked postural changes and absence of pulsations in the larger vessels. Arteriographic and pathologic study revealed that the disease process affected the main vessels. Histologically, the pathologic picture differed from Buerger's original description in that the thrombosis appeared to occur as a primary event.

33 Maijala, P. Death Due to Histamine, *Nord med tidsskr* **16** 1287 (Aug) 1938.

34 Westcott, F. H., and Wright, I. S. Tobacco Allergy and Thromboangitis Obliterans, *J Allergy* **9** 555, 1938.

35 Harkavy, J. Hypersensitiveness to Tobacco and Biopsy Studies of Skin Reactions in Vascular Disease, *J Allergy* **9** 475 (July) 1938.

36 Boyd, A. M. Thromboangitis Obliterans. A Clinical Study, *St Barth Hosp Rep* **71** 151, 1938.

and not as a consequence of intimal disease. Inflammatory or degenerative change in the vessel wall was conspicuous by its absence. In the distal type the initial symptoms were confined to the toes, usually coldness, numbness, ulceration or gangrene. In many cases the symptoms simulated orthopedic disturbances of the feet. The larger vessels were found to be patent, and postural color changes were usually limited to the affected toes. Focal sepsis in the nose or throat was a common finding. Ateriographic examination showed occlusion of the plantar arteries, which were replaced by tortuous collateral channels. Histologically, the lumen was reduced in size as a result of intimal proliferation, although the remainder of the lumen was usually blocked by clot. Fibroses were present in the media. There was no perivascular cuffing of the small vessels in the adventitia. The author was unable to reach definite conclusions as to the etiologic aspects but was impressed with the presence of focal infection in most of the cases of the distal type.

Horton³⁷ reported a statistical study of 948 patients suffering from thromboangitis obliterans. These patients came from every state in the union, except three, and from ten foreign countries. More than twenty-eight different nationalities were represented, 28 per cent of the subjects were Jews. The same fundamental pathologic process was present in all, and the signs and symptoms, as well as the clinical course of the disease, were strikingly similar in all. Ninety-eight per cent of the patients were men. Twenty-one of the patients were women. The mean age of the men was 41.8 years and of the women 38.8 years. Tobacco was used by 93 per cent of the patients. Amputation was undergone by 401 of the 948 patients. Of the Jewish patients, 33.6 per cent underwent amputation, compared with 45.6 per cent of those of other national or racial groups. A study of the cases in which amputation was done for three, five and ten year periods after the onset of the disease indicated that approximately 70 per cent of the patients will go for a period of three years from the onset without the necessity of amputation, whereas only 60 per cent will go for a period of five years and only 40 per cent for a period of ten years.

Of the 175 patients with thromboangitis obliterans known to be dead, 5 were women. It was interesting to note that coronary heart disease ranked first as the cause of death, 47 having died of it, 12 patients died of cerebral hemorrhage, 12 with gangrene or following amputation, and 7 of fatal pulmonary embolism. The others died of known but unrelated causes. Horton expressed the belief that early diagnosis and thorough education of the patient concerning the nature of his disease and the care of his extremities made for a better outlook.

37 Horton, B. T. The Outlook in Thromboangitis Obliterans, *J. A. M. A.* 111: 2184 (Dec. 10) 1938.

From the same clinic, Fatheree and Hines³⁸ reported on 22 patients with thromboangitis obliterans who died, including 9 on whom necropsy was performed. In 16, or 72 per cent of the group, extraperipheral vascular lesions played a dominant role as the cause of death. As in Horton's group, coronary thrombosis was the most common lesion producing death. The average age at death was 41 years. In none of the patients on whom postmortem examination was made were lesions of the visceral arteries found which were typical of those described by Buerger.

In a histopathologic study of the peripheral nerves in a series of 20 cases of thromboangitis obliterans, Barker³⁹ noted various combinations of wallerian degeneration, fibrosis, edema, atrophy, lymphocytic infiltration, inflammation and thrombosis of the vasa vasorum in all but 1 case. Definite correlation was found between wallerian degeneration and the clinical syndrome of ischemic neuritis. In 2 cases in which section of the nerves failed to relieve pain, it was believed that the ischemic inflammatory and degenerative lesions of the nerves had already occurred at levels proximal to the site of section.

Roth, Maclay and Allen⁴⁰ studied the blood of 105 patients with thromboangitis obliterans. The values for serum calcium, serum protein, blood urea, serum lecithin and serum phosphorus were found to be within normal limits. In most instances the blood volume, the hematocrit value and the concentration of fatty acids and of cholesterol in the plasma were found to be normal. In some instances, however, the blood volume was slightly decreased, and the concentration of fatty acids in the plasma and that of cholesterol were slightly increased. The stage of the disease process was not mentioned. Theis and Freeland⁴¹ studied the venous blood of the involved extremity in 7 patients with acute thromboangitis obliterans. They found increased blood viscosity, rapid sedimentation of the cells, rapid coagulation, greatly increased alkalinity, low or normal cell counts and oxygen saturation of arterial blood and a low carbon dioxide content of the blood. These conditions, however, were not noted in 21 clinically improved or recovered patients. Oxygen saturation of the venous blood appeared to follow clinical improvement, being normal when there was freedom from pain.

38 Fatheree, T. J., and Hines, E. A., Jr. Fatal Complications of Thromboangitis Obliterans. A Clinical Study, *Proc. Staff Meet., Mayo Clin.* **13**: 342, 1938.

39 Barker, N. W. Lesions of Peripheral Nerves in Thromboangitis Obliterans, *Arch. Int. Med.* **62**: 271 (Aug.) 1938.

40 Roth, G. M., Maclay, E. V., and Allen, E. V. Blood in Thromboangitis Obliterans, *Arch. Int. Med.* **62**: 413 (Sept.) 1938.

41 Theis, F. V., and Freeland, M. R. The Blood in Thromboangitis Obliterans, *Arch. Surg.* **38**: 191 (Feb.) 1939.

at rest only to return to a high level with recurrence of the disease. This suggested to the authors that a disturbance in the utilization of oxygen is one of the conditions in the complex physiology of the blood and tissue metabolism which are responsible for the acute symptoms. Unlike Roth, Maclay and Allen, they were able to confirm the results of other authors in noting disturbances in phospholipin and cholesterol metabolism. Low basal metabolic rates were noted in all.

They also investigated in 6 cases the etiologic role of typhus fever in thromboangitis obliterans. All of the cutaneous tests with antigen supplied by Goodman were negative.

Hausner and Allen⁴² concluded from a study of reports of 23 cases of thromboangitis obliterans collected from the literature, in which there occurred both cerebral and peripheral involvement, that lesions of the cerebral vessels, while not always characteristic of thromboangitis obliterans, may be present in persons with this disease of the extremities who do not have syphilis, hypertension, diabetes or other detectable causes for cerebrovascular lesions. They have observed 11 patients with thromboangitis obliterans involving the extremities in whom there was evidence of vascular lesions involving the brain. These were encountered in a study of 500 patients with peripheral involvement. The duration of the peripheral disease in this group varied from five months to twenty years. The ages of the patients varied from 35 to 59 years. In most of the patients the cerebral complications occurred following the onset of the peripheral disease. The cerebral lesions preceded the peripheral symptoms in only 3 patients. In these 3 hemiplegia was present one, two and fourteen years, respectively, before the onset of the peripheral symptoms. Thromboangitis obliterans must therefore be suspected in cases of cerebrovascular disease of obscure cause. The main neurologic symptom was hemiplegia, which occurred transiently once, several times or permanently. Some patients showed confusion, disorientation, aphasia and loss of memory, symptoms which frequently cleared up entirely. Hemianopia, present in 2 patients, disappeared in 1 patient following sympathectomy. The symptoms depended chiefly on the location of the cerebral lesion. This complication may be noted more frequently if attention is directed to it. This study emphasized that cerebrovascular complications may occur in cases of thromboangitis obliterans and may precede evidence of thromboangitis obliterans of the extremities. It is also apparent that peripheral thromboangitis obliterans may be the least serious part of a disease which may be disabling and in which life may be terminated by cerebral or cardiac involvement.

42 Hausner, E., and Allen, E. V. Cerebrovascular Complications in Thromboangitis Obliterans, *Ann Int Med* 12 845, 1938

Cases in which thromboangitis obliterans was associated with diabetes were reported by Collens and Wilensky (1 case) ⁴³ and Helm and Horton (1 case) ⁴⁴. The former authors resorted to biopsy to establish the diagnosis. Cases of thromboangitis obliterans in women were reported by Millman ⁴⁵ and Robinson ⁴⁶. The authenticity of Robinson's case is doubtful from the evidence supplied. The condition was associated with the menopausal syndrome.

ARTERIOSCLEROSIS

New concepts of the biologic aspects of arteriosclerosis were published in an excellent book by Winternitz, Thomas and LeCompte ⁴⁷. The assumption which guided these studies was that blood extravasating within the wall, especially the intima, of the aorta and large arteries may be at least one source of the lipoidal deposit and the cause of the formation of the atheromatous plaque which characterizes human intimal arteriosclerosis. This assumption was based on the knowledge that lipoidal deposits at other sites may have their origin in extravasated blood and on the frequent observation of vascularization and hemorrhage within the lesions of human simple intimal arteriosclerosis. It was recognized by the authors that the mere demonstration of blood vessels and of extravasated blood in arteriosclerotic plaques does not constitute proof of a primary causal relationship between the former and the latter. The reverse may be true, for the vascularization and hemorrhage could be, as most students of the subject have thought, secondary to the lipoidal deposit. The authors' view has found support in their convincing demonstration by special technical methods of an "extensive vascular network" in the intima of normal blood vessels of a number of animal species other than man. The origin of the anastomosing intimal vasa has been demonstrated to be from (1) the adventitia, (2) the region of orifices of branches and (3) the lumen of the vessel. Two outstanding weaknesses must be explained before the significance of these studies can be fully recognized and the results applied to the problem of the origin of simple arteriosclerosis in man. The first difficulty is that, while the demonstration of anastomosing channels in

43 Collens, W. S., and Wilensky, N. D. Thromboangitis Obliterans in a Diabetic, *Am Heart J* **17** 624 (May) 1939.

44 Helm, S., and Horton, B. T. Thromboangitis Obliterans Associated with Diabetes Mellitus, *Ann Int Med* **12** 1493 (March) 1939.

45 Millman, S. Thromboangitis Obliterans in Woman. Report of a Case, *Am Heart J* **15** 746 (June) 1938.

46 Robinson, S. K. Thromboangitis Obliterans in a Woman with the Menopausal Syndrome, *M Rec* **149** 233, 1939.

47 Winternitz, M. C., Thomas, R. M., and LeCompte, P. M. *The Biology of Arteriosclerosis*, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

the intima of normal arteries of different animal species can be accepted, it is a fact that the arteriosclerosis which occurs in such animals is most commonly medial, characterized by degeneration and calcification of this coat and not by atheromatosis, which is an important part of the lesion of simple intimal arteriosclerosis in man. The second difficulty is that these authors have failed to demonstrate anastomosing channels in the intima of the normal human aorta and arteries, yet it is in this very location that simple arteriosclerosis develops in man. Until these obstacles are successfully overcome there can be no strict application of the results of this work to the complex problem of the genesis of human arteriosclerosis.

Leary⁴⁸ questioned the etiologic role of intimal hemorrhage in arteriosclerosis. It was his opinion that the normal intima was not vascularized and that vascularization occurred only in connection with vascular lesions in which repair had taken place. He reasoned that since the vessels arose only as a result of a repair process and since the lesions were of the advanced atherosclerotic type the hemorrhages from such vessels must be a late phenomenon and therefore not of etiologic importance. He expressed the belief that the cholesterol found in atherosclerotic lesions was not a deposit from the blood of these hemorrhages, because of the minute amounts of this material in the original hemorrhage. He offered the opinion that the cholesterol was most likely transported to the site in macrophages or as free or ester cholesterol in the blood.

Hines⁴⁹ made a clinical study of 280 patients with thromboarteriosclerosis obliterans. The ratio of males to females was found to be 6 to 1. The age range was from 35 to 94, 70 per cent of the patients being in the fifth, sixth and seventh decades of life. No significant difference in racial incidence was noted. In only 3 patients was either the radial or the ulnar artery occluded. This was considered an important finding because of the contrast with thromboangitis obliterans, in which involvement of the vessels of the upper extremities is not uncommon. No correlation could be made between the extent of calcification shown by roentgenograms and thrombosis with occlusion, although the incidence of calcification among men was 69 per cent and among women 31 per cent. Diabetes was present in 20.3 per cent of the patients. In this group the incidence of ulcer and gangrene was greater than in the nondiabetic group. Ischemic neuritis was noted in 8

48 Leary, T. Vascularization of Atherosclerotic Lesions, *Am Heart J* **16** 549, 1938.

49 Hines, E. A., Jr. Thromboarteriosclerosis Obliterans. A Clinical Study of Two Hundred and Eighty Cases, *Proc Staff Meet, Mayo Clin* **13** 694 (Nov 2) 1938.

per cent and paresthesias in 5 per cent. Hypertension was noted in 35 per cent. However, this figure was considered low, because many had a latent form of hypertension, as demonstrated by changes in retinal arteries and by cold pressor tests. Of the 116 patients about whom there was satisfactory follow-up information, 54.6 per cent died within three years after their first admission. The majority died in a manner suggestive of coronary thrombosis. The incidence of deaths was not appreciably higher in the group of patients who had diabetes. The incidence of amputation was found to be 25 per cent, a figure considered low because of a presumed additional 5 per cent who might have had amputation elsewhere.

Kramer⁵⁰ studied the peripheral circulation in 100 diabetic persons selected at random. Taking the group as a whole, he found the incidence of sclerosis to be 38 per cent. However, there was a marked increase in the incidence with each decade. Hypertension was present in 28 per cent of those showing evidence of sclerosis. Hyperglycemia did not appear to influence the development of sclerosis. Elevated levels of blood cholesterol were found for only 23 per cent of all the diabetic patients and only 21 per cent of the arteriosclerotic ones had elevated lipid readings. Roentgen studies of the lower extremities revealed calcium in the walls of blood vessels in 63 per cent of the patients in the arteriosclerotic group. Fourteen patients showing no evidence of sclerosis as demonstrated by this method had other indications of vascular damage. All the patients in the arteriosclerotic group showing normal responses in histamine tests excepting 2 had correspondingly good oscillometric readings. Sixty-seven per cent showed normal responses to histamine. Kramer expressed the opinion that many methods of study were necessary to diagnose arteriosclerosis. The results of histamine studies were a most reliable guide to presence or absence of sufficient collateral circulation. The number of patients having poor or no pulsations of the peripheral vessels of the lower extremities compared favorably with the number showing a poor oscillometric index. The ophthalmologic examination of the fundi, the roentgen study of the lower extremities and the blood pressure readings demonstrated a relatively equal incidence of arteriosclerosis.

Stroud and Shumway⁵¹ noted the occurrence of intermittent claudication in a certain number of persons subject to coronary occlusion. In a series of 57 patients with coronary occlusion 7 had inter-

50 Kramer, L. I. Various Methods of Determining the Early Diagnosis of Arteriosclerosis in Diabetes, *New England J. Med.* **220**: 278 (Feb. 16) 1939.

51 Stroud, W. D., and Shumway, N. P. Intermittent Claudication as an Early Symptom of Cardiovascular Disease, *Pennsylvania M. J.* **41**: 894, 1938.

mittent claudication, as compared with 1 in a series of 106 patients without heart disease. They also noted that patients with hypertension were more likely to complain of cramps in their legs at night than normal persons.

Randall⁵² studied the lipid composition of nerves from arteriosclerotic and diabetic subjects. The peripheral nerves from these subjects showed marked decreases in phospholipids, cholesterol and cerebrosides and an increase in neutral fat but no significant change in water content. The posterior tibial nerve showed more extensive change from normal than the sciatic and the latter more than the femoral. The femoral, sciatic and posterior tibial nerves from normal subjects did not show significant differences in composition. The greater extent of chemical change in the more distal parts of the nerves was indicative of an inadequate blood supply and concomitant anoxemia resulting in decomposition of the lipid constituents.

Millet⁵³ described 2 fatal cases of diabetic gangrene of the face. In both cases the lesions in their early stages resembled erysipelas, with later a breakdown of tissue.

PERIARTERITIS NODOSA

Articles on this subject consist mainly of case reports, each bearing on some etiologic phase of the disease. Berger and Weitz⁵⁴ reported a case in which periarteritis nodosa developed in an allergic person while this person was under observation. An antemortem diagnosis was made on the results of a biopsy of muscle. The authors believed that this case substantiated the theory of the allergic background of this disease. Becker⁵⁵ reported the case of a boy of 13 admitted with a tonsillar abscess in whom later cardiac insufficiency developed with fatal termination. Autopsy confirmed the diagnosis. Cleland⁵⁶ observed periarteritis nodosa in 3 of 4,000 autopsies. In 1 of these cases rheumatic vegetations were present on the mitral valve. He stated the opinion that there was a definite relation between periarteritis nodosa and rheumatic fever and that it was possible that the former disease was in some cases an allergic response to the agent

52 Randall, L. O. Changes in Lipid Composition of Nerves from Arteriosclerotic and Diabetic Subjects, *J Biol Chem* **125** 723 (Oct) 1938

53 Millet, J. Diabetic Gangrene of the Face, *J A M A* **112** 1143 (March 25) 1939

54 Berger, S. S., and Weitz, M. A. Periarteritis Nodosa, *J Allergy* **9** 489 (Aug) 1938

55 Becker, W. Ueber Periarteritis nodosa, *Med Klin* **34** 869, 1938

56 Cleland, J. B. Periarteritis Nodosa. Report of Two New Cases, *M J Australia* **1** 847, 1938

of rheumatic fever Matras⁵⁷ described a case in which periarteritis nodosa occurring in the vessels of the skin was associated with extensive hemorrhages and gangrene

THROMBOSIS

LeFevre⁵⁸ reported the case of a boy of 16 in whom thrombosis of the right posterior tibial artery developed following a simple contusion inflicted by a golf ball Symptomatic and objective improvement followed the administration of passive vascular exercise Adson and Allen⁵⁹ reported thrombosis of the arteries of the right upper extremity secondary to the presence of an anomalous first rib Watkins⁶⁰ reported gangrene of various digits in both upper and lower extremities of an infant 11 weeks old He held, because of the sequence of events leading to the gangrene, that the condition was most likely arteritis secondary to recent streptococcic infection producing thrombosis of the phalangeal arteries An embolic phenomenon seemed unlikely because of the nature of the infant's illness

RAYNAUD'S DISEASE

Lewis⁶¹ compared the pathologic changes in the arteries of the fingers in warm-handed people with those in patients with so-called Raynaud's disease The warm-handed adults, used as controls, usually showed distinct intimal thickening in the digital arteries increasing with age General thickening was the rule after the age of 50 The thickening consisted of hyperplasia of the intimal tissues After 60 years the thickening was conspicuous In digital arteries subject to intermittent spasm of the type exemplified in the mildest form of so-called Raynaud's disease there was no more intimal thickening than was to be found in the arteries of warm-handed people of similar age In digital arteries of the same type but with spasm of greater severity more intimal thickening than usual was found, but it was not more than that found in many subjects presenting no symptoms Attacks of discoloration of the fingers in these cases were ascribed to

57 Matras, A Zur kutanen Form der Periarteritis nodosa, Wien klin Wchnschr **51**:991 (Sept 16) 1938

58 LeFevre, F A Arterial Thrombosis Following Simple Contusion, Am Heart J **17** 111 (Jan) 1939

59 Adson, A W, and Allen, E V Vascular Clinics VI Thrombosis of Arteries of the Right Upper Extremity Resulting from Anomalous First Rib, Proc Staff Meet, Mayo Clin **13** 637 (Oct 5) 1938

60 Watkins, A G Gangrene of the Extremities in an Infant, Arch Dis Childhood **13** 366, 1938

61 Lewis, T The Pathological Changes in the Arteries Supplying the Fingers in Warm-Handed People and in Cases of So-Called Raynaud's Disease, Clin Sc **3** 287, 1938

overaction of the muscular wall. Hyperplasia of the media was not found in any of them, the digital arteries were normally very muscular. In 2 cases of intermittent spasm in which the finger tips presented the scars of small healed necroses, obstructive disease of the digital arteries was discovered. The arterial wall generally presented intimal hyperplasia, the lumens being conspicuously reduced or actually occluded by new cellular tissue or by recent or organized thrombus. The conspicuous lesions were present in scarred and unscarred fingers. In cases of intermittent spasm in which the fingers presented unhealed necroses, thrombotic obstruction of the digital arteries was the rule. The thrombi were seen in various stages of organization. In cases of bilateral discoloration and necrosis of fingers, in which there had been no previous attacks of discoloration, the predominant lesion was thrombosis, and the thrombi were in various stages of organization. Similar lesions were found in necrosed and nonnecrosed fingers in these cases. Lewis suggested that in many patients experiencing attacks of discoloration leading to necrosis of the fingers, symptoms were determined by an initial thrombosis. He was not able to present evidence that attacks of digital arterial spasm produced thickening of the medial or intimal coats of the digital arteries, he thought, however, that it might lead to thrombosis. In patients with diffuse scleroderma presenting attacks of discoloration of the fingers there was an occlusive disease of the digital arteries. In the intimal thickening, hyperplasia of the original tissues and connective tissue growth play conspicuous parts. Organizing thrombi may be found in the lumen. He expressed the belief that in the presence of a full radial pulse failure to elicit any capillary pulsation at the tips of the fingers by adequately heating the hand indicated a considerable reduction or obliteration of the lumens of digital arteries by structural disease. The same author⁶² studied 6 cases of Raynaud's disease shortly after preganglionic sympathectomy. Discoloration of the fingers occurred spontaneously or was induced within a few days after the operation in 3 cases. In 2 of the remaining 3 cases abnormal reactions to cold were produced with difficulty before operation, but easily after the operation. He expressed the belief that preganglionic sympathectomy did not bring the fingers to a normal state, as a local abnormality remained which could be displayed in a measure related to the abnormality displayed before operation. He offered the opinion that the attacks in Raynaud's disease were due not to excessive action of the vasomotor system but to a local fault and that in some cases this was an occlusive structural disease, as mentioned. There appears to be an

62 Lewis, T. Raynaud's Disease and Preganglionic Sympathectomy, *Clin. Sc.* 3: 321, 1938.

increased susceptibility of the vessels to cold. He showed that full vasodilatation declined slowly during a period of a week after operation. Houston and Johnson⁶³ reported the case of a young woman suffering from Raynaud's disease who had calcified nodules in the soft tissue of her fingers.

ANGIOSPASTIC DISTURBANCES

Gifford and Marquardt⁶⁴ described a type of central retinopathy affecting young or middle-aged persons with little or no increase in general blood pressure. In all of the patients examination revealed definite signs of peripheral vascular spasm. The authors concluded that the ocular symptoms were purely angiospastic, on the following grounds: A high degree of arterial spasm was found elsewhere, the attacks of blindness were transient, these attacks were frequent with definite ophthalmoscopic findings, and antispasmodic treatment resulted in complete or almost complete recovery of function. The treatment consisted in administration of antispasmodic drugs, as the nitrites, of typhoid vaccine or of tissue extract, along with avoidance of tobacco, exposure to cold and psychic trauma. Perry and Davie⁶⁵ reported symmetric peripheral gangrene of the lower limbs developing shortly before death in a person with congestive heart failure as a result of hypertensive heart disease. They discussed the possibility that this rare occurrence was due to reflex vasoconstriction leading to redistribution of the circulating blood in an attempt to protect the vital organs from the effects of a diminished cardiac output. At autopsy the aorta presented a moderate degree of atheroma, but the iliac, femoral and popliteal arteries showed no obstruction on either side. Warembourg, Linquette and Ravaut⁶⁶ noted that arteriolar spasm occurred frequently in patients with cardiac insufficiency. Various tests were made on 64 patients with heart disease to demonstrate this phenomenon. The relationship between angiospastic conditions and hypocalcemia was again discussed by Norman⁶⁷. Cases in which migraine was associated with various peripheral vasospastic phenomena, such as blanching or paresthesias of the fingers, were discussed. He held that these headaches were thus angiospastic in nature. A large number of the patients

63 Houston, C. J., and Johnson, E. A Case of Unusual Calcium Deposition Due to Raynaud's Disease, *Canad. M. A. J.* **39** 60, 1938.

64 Gifford, S. R., and Marquardt, G. Central Angiospastic Retinopathy, *Arch. Ophth.* **21** 211 (Feb.) 1939.

65 Perry, C. B., and Davie, T. B. Symmetrical Peripheral Gangrene in Cardiac Failure, *Brit. M. J.* **1** 15 (Jan. 7) 1939.

66 Warembourg, H., Linquette, M., and Ravaut, J. Arteriolar Spasm in Cardiac Insufficiency. Its Therapeutic Consequences, *Presse méd.* **46** 1761, 1938.

67 Norman, G. F. Blood Calcium. Its Relation to Certain So-Called Angiospastic Conditions, *West. J. Surg.* **46** 513 (Oct.) 1938.

were relieved by no other therapy than that of giving viosterol to raise the blood calcium

CIRCULATION AND ARTHIRITIS

Kling⁶⁸ studied the joints and vessels of the lower extremities of patients who had undergone amputation for gangrene. The group included 3 patients with thromboangitis obliterans and 10 with arteriosclerosis. In both types of patients the vessels of the extremities showed advanced lesions. In those with thromboangitis obliterans the synovial vessels were found to be frequently involved with no hypertrophy of the synovial membrane. In those with arteriosclerosis, however, the vessels of the synovia were normal or moderately affected and in only 2 were the membranes definitely hypertrophied. Subacute synovitis of the ankle and knee joints was present in a patient with thromboangitis obliterans, and in another venous congestion of the membrane was noted. Pronounced osteoarthritis was present in only 2 of the patients with arteriosclerosis. In all patients past 40 years of age slight erosion of the articular cartilage was noted which corresponded to that found in a control group of similar age. The author was thus unable to substantiate the vascular theory of osteoarthritis.

ARTERIOVENOUS ANEURYSMS

Reid and McGuire⁶⁹ presented another series of 30 aneurysms of which 21 were arteriovenous and 9 cirroid. Clinical observations, surgical procedures and experimental studies on dogs were presented. No aneurysm in the entire series proved fatal. There were 8 arteriovenous aneurysms which had caused definite cardiac damage, with 2 there was severe cardiac decompensation. Of the 9 cirroid aneurysms, 2 were associated with evidences of some cardiac damage. In every instance in which the heart was demonstrably affected, closure or excision of the fistula was followed by cardiac improvement. In the walls of the artery and vein opposite the fistula extensive calcification was noted. In 11 cases definite enlargement and thinning of the wall of the proximal artery were noted. In many cases the wall of the involved vein was definitely hypertrophied. There was no positive evidence that the circulation time was definitely affected by the fistula. The authors' studies failed to confirm the observations of Holman and others who reported a large increase in blood volume in the presence of arteriovenous aneurysm. Slowing of the pulse rate when the fistula was closed was observed in 10 cases as well as in experiments on ani-

68 Kling, D. H. The Significance of Peripheral Circulatory Disturbances for the Development of Osteo-Arthritis, *Am J M Sc* **197** 358 (March) 1939

69 Reid, M. R., and McGuire, J. Arteriovenous Aneurysms, *Ann Surg* **108** 643 (Oct) 1938

mals The extent of this slowing of pulse rate varied greatly and seemed to be directly related to the seriousness of the cardiac damage and the size of the fistula Venous pressures appeared to be unaffected by arteriovenous aneurysms unless there was some evidence of cardiac decompensation, at which time the changes in venous pressures were similar to those which normally occur in cardiac decompensation A rise in both systolic and diastolic pressure following closure of arteriovenous fistula was observed in 13 cases An extensive collateral circulation around an arteriovenous fistula was demonstrated in 6 instances This extensive collateral circulation makes the occurrence of gangrene after excision of chronic arteriovenous fistula practically unknown The circulation distal to the fistula may be impaired, as evidenced by absence of pulses, coldness of the part, cyanosis and occasional chronic ulcers Nerve paralyses associated with the arteriovenous condition occurred in 4 cases Intracranial arteriovenous aneurysms developed in 3 cases, pulsating exophthalmos in 2 and a fistula between the ophthalmic vessels behind the eyeball in 1

ERYTHROMELALGIA

Smith and Allen⁷⁰ held that "erythermalgia" was a more descriptive term than "erythromelalgia" for the syndrome of heat, redness and pain of an extremity The latter, they said, was not entirely adequate because it did not denote the importance of heat The rather definite clinical picture was described by the authors as a syndrome affecting one or more extremities and consisting of discoloration and distress, both of which were dependent entirely on the temperature of the skin, an increase of which constituted the third component The condition might occur as a primary disturbance, or it might be secondary to such a condition as polycythemia vera The diagnosis depended on the establishment of a close relationship between the occurrence of the distress and the temperature of the skin When the temperature of the skin increased above a critical point, usually 32 C, the distress occurred, and when it decreased below this point the distress disappeared They believed that the distress itself resulted from a susceptibility of the skin to increased temperatures, a condition which did not occur in normal persons

A case of erythromelalgia associated with chronic gout was described by Markel⁷¹ Relief was obtained for two years by an intravenous injection of typhoid vaccine

70 Smith, L A, and Allen, E V Erythermalgia (Erythromelalgia) of the Extremities, *Am Heart J* **16** 175, 1938

71 Markel, J Erythromelalgia Report of Case of Its Association with Chronic Gout with Relief of Symptoms for Two Years After Intravenous Administration of Typhoid Vaccine, *Arch Dermat & Syph* **38** 73 (July) 1938

ACROCYANOSIS

Day and Klingman⁷² reported a study of the effect of sleep on the cutaneous temperature of a 6½ year old girl with acrocyanosis. During sleep there was spontaneous warming and reddening of the hands and feet. Under these conditions the hands responded in a parallel way with the rest of the body to warm and cold foot baths. Local cooling of the hand under induced sleep did not cause vasoconstriction. The authors expressed the belief that their studies supported the theory of a central rather than a local origin of this abnormal vasomotor tone. Microscopic studies of the capillaries at the nail base showed sluggish blood flow and venous dilatation.

GLOMUS TUMOR

Grauer and Burt⁷³ reported 2 cases of glomus tumor located on the penis. This report was of interest not only because of the unusual site but because in 1 case the onset occurred at 1 year of age.

Doane⁷⁴ reported an additional case of a glomus tumor on the finger of a 31 year old woman.

PHLEBITIS AND THROMBOSIS

Many articles have been published on this subject during the current year. Few new ideas have been presented. Arterial symptoms secondary to phlebitis of the extremities were discussed by many authors (Uggeri and Massone⁷⁵, Audier and Haimovici⁷⁶, Gregoire⁷⁷, Zehnder⁷⁸, Ochsner and DeBakey⁷⁹). Uggeri and Massone⁷⁵ expressed the opinion that ischemia might be caused by one of three conditions, namely, arteritis from dissemination of phlebitis, secondary arterial spasm or a combination of both. Audier and Haimovici⁷⁶

72 Day, R, and Klingman, W O. The Effect of Sleep on Skin Temperature Reactions in a Case of Acrocyanosis, *J Clin Investigation* **18** 271 (May) 1939.

73 Grauer, R C, and Burt, J C. Unusual Location of Glomus Tumor, *J A M A* **112** 1806 (May) 1939.

74 Doane, C P. Glomus Tumor (Glomangioma), *J A M A* **112** 1049 (March 18) 1939.

75 Uggeri, C, and Massone, A. Arterial Symptoms from Phlebitis of Limbs, *Arch ital di chir* **49** 429 (Sept) 1938.

76 Audier, M, and Haimovici, H. Les gangrenes des membres d' origine veineuse, *Presse med* **46** 1403, 1938.

77 Gregoire, R. La phlebite bleue (phlegmatia cærulea dolens), *Presse med* **46** 1313, 1938.

78 Zehnder, M. Die Claudicatio venosa der oberen Extremitäten als Symptom, *Arch f klin Chir* **192** 354, 1938.

79 Ochsner, A, and DeBakey, M. Treatment of Thrombophlebitis by Novocain Block of Sympathetics, *Surgery* **5** 491, 1939.

discussed venous gangrene, citing many cases reported elsewhere. In each case autopsy demonstrated an intact arterial system. Although the most logical cause appeared to be secondary arterial spasm, other possibilities were discussed. They offered the opinion that such gangrene could develop from mechanical blockage due to complete obliteration of all the veins or from stasis in terminal capillary beds resulting from a disease process in the venous loops. At autopsy no definite occlusion could be demonstrated as a direct cause for the gangrene. Gregoire⁷⁷ discussed a definite type of superficial phlebitis which was characterized by an excessive amount of vasospasm.

Zehnder⁷⁸ studied 8 cases of venous claudication in the upper extremities, resulting from strain, by means of venograms and infra-red photographs. He was unable to demonstrate venous thrombosis in all of the cases. He showed that the symptoms could be produced by vasomotor changes, muscle swelling or muscle contraction. Roelsen⁸⁰ reported 7 cases of traumatic thrombosis of the axillary-subclavian vein. The condition was characterized by acute venous stasis, in part recurrent, manifested by marked venous dilatation and diffuse swelling of the upper extremity. A case of traumatic thrombosis of the deep palmar vein was reported by Snyder and Snyder.⁸¹

The relationship between serum sodium chloride and venous thrombosis was studied by Russo.⁸² In 44 cases of thrombosis he found the sodium chloride content of the serum to be within normal limits, thus he rejects the suggestions of other authors that chloride deficiency is a cause of spontaneous thrombosis. A review of cases of hypochloremia and of experiments on animals in this connection failed to disclose a tendency toward thrombosis. The author expressed the opinion that dehydration resulting from withdrawal of sodium chloride is a problem that concerns not the blood vessels but the tissues. Consequently it has no accelerating effect on blood coagulation and is not a factor in the genesis of venous thrombosis. Moreover, the sodium chloride content of the blood has little influence on the viscosity of the blood. The author expressed the belief that venous thrombosis in patients with heart disease is not connected with dehydration procedures. According to Dougal,⁸³ trauma of tissue and sepsis are the two primary causative

80 Roelsen, E. So-Called Traumatic Thrombosis of Axillary-Subclavian Veins, *Hospitaltid* **81** 889 (Sept.) 1938.

81 Snyder, M. H., and Snyder, W. H., Jr. Traumatic Thrombosis of Deep Palmar Vein, *J. A. M. A.* **111** 2007 (Nov. 26) 1938.

82 Russo, G. Sodium Chloride Content of Serum and Changes in Blood During Venous Thrombosis, *Med. Klin.* **35** 233 (Feb.) 1939.

83 Dougal, D. Ætiology of Thrombosis and Embolism, *J. Obst. & Gynaec. Brit. Emp.* **45** 405 (June) 1938.

factors in thrombosis and embolism. Slowing of the circulation, in his opinion, is the most important predisposing cause, as thrombosis rarely occurs if the blood flows freely.

Veal,⁸⁴ since his recent publication of venographic observations in 20 cases of swelling of the arm following radical removal of the breast, has observed 26 additional cases, a total of 46 cases of swelling following operation. Twenty-two patients who did not experience swelling of the arm after such operation were studied in order to determine the possible extent of the venous obstruction existing before edema occurred. Venographic studies supplemented with determinations of venous pressure proved valuable as a means of differentiating between the several forms of arm swelling following radical amputation of the breast. Simple lymphatic edema was the least frequent cause of swelling of the arm after such an amputation. He believed that this form of edema might result from recurrent lymphangitis, cellulitis or cutaneous metastases. The deep veins of the arm were not primarily involved and remained patent. Edema resulting from obstruction of the axillary-subclavian vein was by far the most common cause of swelling of the arm following operation. The most frequent cause of the venous obstruction was a recurrence of the malignant growth along the course of the veins. In some cases the venous occlusion resulted from benign scar formation. In others the axillary part of the vein was occluded by the sharp angulation of its course when the arm was dependent, because of the fixation of the floor of the axilla. The venous obstruction produced a local increase in the venous pressure, and fluid escaped into the tissues. Lymphatic stasis was a secondary result of the venous obstruction and if prolonged led to permanent blockage of the lymphatic flow. Infection was prone to develop, and when it did led to further obstruction and caused a greater degree of swelling. The skin then became thickened, presenting the typical picture of lymphatic edema.

Monteiro⁸⁵ described his technic for making lymphangiograms on various animals, using thorium dioxide as a contrast medium. The technic was much like that used in the injection of the lymphatics in cadavers. He demonstrated in animals that sympathectomies favor, as in the case of arteries, the reestablishment of the lymphatic circulation after the interruption of the large trunks by the development of a large number of derivative passages.

84 Veal, J. R. Pathologic Basis for Swelling of the Arm Following Radical Amputation of the Breast, *Surg., Gynec. & Obst.* **67** 705 (Dec.) 1938.

85 Monteiro, H. Lymphangiography in the Living. Method, Results and Applications, *Bruxelles-med.* **19** 205 (Dec.) 1938.

TREATMENT

The present day therapy of peripheral vascular diseases is not yet entirely satisfactory. This is evident in the multiplicity of procedures, drugs and mechanical devices now used and in the fact that many such procedures have fallen into disrepute after a relatively short use.

Wollaeger, Allen and Ghormley⁸⁶ stressed the importance of persistent treatment of patients suffering from thromboangitis obliterans, using 2 illustrative cases. In both cases major amputation was rejected in favor of conservative management. Although the patients were submitted to months of persistent medical management the end results were so satisfactory that the authors felt justified. Better and adequate conservative treatment, with less haste to amputate, was shown to be very desirable in many cases.

Wolffe⁸⁷ reported beneficial results in 60 patients with diabetic and 40 with nondiabetic arteriosclerotic gangrene from the use of pancreatic (enzyme free) tissue extract. Complete healing was obtained in 75 per cent of the patients. Injections were repeated whenever there was a complaint of pains or cramps in the legs and difficulty in walking. Many of his patients had been under observation for years. To many of them additional remedies were given simultaneously, such as papaverine hydrochloride, heat, diets low in cholesterol, insulin when needed, and alcohol. He stated that pancreatic extract seemed not only to produce an early arrest of pathologic processes but also to stimulate more rapid and more complete repair than other conservative means.

The treatment of erythromelalgia (or erythermalgia) was not found to be uniformly successful by Smith and Allen⁷⁰. They found it important to determine whether there was any condition, such as polycythemia, to which erythermalgia might be secondary. Under such a circumstance the treatment of the syndrome affecting the extremities would be the treatment of the condition which produced it. Surprisingly, in some cases acetylsalicylic acid in amounts of 10 grains (0.65 Gm) produced marked relief, persisting for as long as several days. No adequate explanation of this was available. Some symptomatic relief could be obtained by avoiding procedures that cause vasodilatation in the extremities. Avoidance of exposure of the feet to warmth, as in riding in the front seat of an automobile, alleviated some of the distress, as well as the use of light socks or stockings and of sandals or perforated shoes. When simple measures failed, it became

86 Wollaeger, E. E., Allen, E. V., and Ghormley, R. K. The Value of Persistence in the Treatment of Thromboangitis Obliterans. Report of Two Illustrative Cases, *Minnesota Med* **22** 305 (May) 1939.

87 Wolffe, J. B. Pancreatic Extract (Enzyme-Free) in the Treatment of Diabetic and Arteriosclerotic Gangrene, *Am J Surg* **43** 109, 1939.

necessary in some cases to anesthetize the skin of the feet by section by crushing or by injecting alcohol into such peripheral nerves as the posterior tibial, peroneal and sural. The logical procedure appeared to be to attempt to desensitize the skin to heat.

Sedwitz⁸⁸ found the paraffin boot to be a valuable adjunct in the therapy of peripheral vascular diseases. He found that it produced and maintained heat in a diseased extremity. The temperature of the skin and oscillometric readings were found to be increased as compared with those of normal persons when the boot was used prior to treatment by intermittent venous occlusion. Montgomery and Starr⁸⁹ described in detail the construction of four well known mechanical devices for use in the therapy of peripheral vascular disorders. Each had been selected because of low cost and efficiency, having been used successfully by these physicians for periods of from one to four years. These devices consist of (1) a simple thermoregulator for maintaining an optimal temperature in a foot cradle, (2) an inexpensive apparatus for giving drugs by iontophoresis, (3) a bed so constructed that the patient is able to be comfortable with the legs in a dependent position and (4) an original small suction pressure apparatus to be inserted on the fingers. With the latter apparatus, reddening of the skin in the suction phase with blanching during pressure was easily demonstrated. This was found to be useful for home treatment by persons suffering from diseases confined to the fingers.

The Council on Physical Therapy of the American Medical Association⁹⁰ accepted the Sanders vasocillator as an adjunct in the therapy of peripheral vascular diseases. The vasocillator is a bed which is capable of oscillating up and down at a regular cycle, which can be adjusted at will. It is capable of giving exercise similar to Buerger's exercise to persons unable to perform active movements. The patient learns to sleep in the bed, thus making it possible for the exercise to be continued over long periods. It was the opinion of the Council that this bed had a limited therapeutic usefulness and that no more could be expected from it than could be achieved by the conventional Buerger exercise.

Veal and McCord⁹¹ studied the oxygen saturation of venous blood after true reactive hyperemia and after intermittent venous occlusion.

88 Sedwitz, S. H. The Paraffin Bath in Peripheral Vascular Disease, *Arch Phys Therapy* **20** 165, 1939.

89 Montgomery, H., and Starr, I. Four Physiotherapeutic Devices for the Treatment of Peripheral Vascular Disorders, *Am J M Sc* **197** 485 (April) 1939.

90 Sanders Vasocillator, Acceptable, report of the Council on Physical Therapy, *J A M A* **111** 2016 (Nov 26) 1938.

91 Veal, J. R., and McCord, W. M. Blood Oxygen Changes Following Intermittent Venous Occlusion, *Am Heart J* **17** 401 (April) 1939.

The test was conducted on 11 healthy male subjects, a blood pressure cuff being used for compression. Studies were made on the arm, blood being drawn from the antecubital veins under oil. The maintenance of complete compression over periods of five to eight minutes was followed in 9 of 11 cases by a definite rise in the oxygen saturation of the venous blood one minute after its release. In most cases the elevation was maintained at the end of three minutes. Intermittent venous occlusion, on the other hand, even in the presence of a normal circulatory system, was usually followed by a lowering of the oxygen saturation of the venous blood at the end of one and three minutes after release. In the latter experiment cuff pressures varied from 60 to 80 mm of mercury, with a ratio of compression to release of 2:2 and 2:1. The authors assumed from these experiments that reactive hyperemia increased the blood flow and also increased the volume of the flow. Intermittent venous occlusion, on the other hand, produced no increase in rate or in volume of blood flow, but the authors could not deny the possibility of some chemical changes occurring in the tissues incidental to the venous congestion.

A similar study was made by Harpuder and Stein,⁹² who studied the effect of mild hyperemia on the extremities of healthy and diseased persons. For each subject the venous compression was less than 40 mm of mercury and lasted forty minutes, being then followed by release. Studies of oxygen, carbon dioxide, lactic acid and total oxygen capacity of venous blood were made. In healthy adults the oxygen content of the venous blood was definitely decreased, whereas in patients with occlusive vascular disease it was increased. Insignificant changes of the carbon dioxide content occurred in healthy persons, however it was decreased in only 3 of those with diseased extremities. Oxygen capacities and lactic acid values changed very little. As these values changed slightly and returned to normal levels on release, the authors concluded that hyperemia did not occur after release of venous pressures below 40 mm of mercury. Studies with the capillary microscope during compression showed the capillaries to dilate and increase in number, but the flow appeared to be slower. Clinically, improvement was noted in patients suffering from old indolent ulcers, but those with gangrene, cellulitis and pain at rest were only slightly improved.

Kountz⁹³ found the suction pressure form of therapy to be of little value in his hands. He experimented with this type of machine on the extremities of persons who had just died. Blood flow was maintained

⁹² Harpuder, K., and Stein, I. Therapeutic Value of Passive Hyperemia in Peripheral Vascular Disease, *Arch Phys Therapy* 20:9 (Jan) 1939.

⁹³ Kountz, W. B. Re-Establishment of the Circulation in Extremities, *Arch Phys Therapy* 20:157 (March) 1939.

by a profusion apparatus using especially prepared animal blood. Under these experimental conditions he noted that a continuous flow could be obtained only if the venous system was full and that such a flow was impossible when the venous system was collapsed, even though the arterial pressure was increased several times. He also noted, especially in diseased extremities, that the obstruction to the passage of blood could be relieved by perfusion of hypertonic saline solution. This he explained by the idea that the saline solution probably had a dehydrating influence on the swollen capillary endothelium. Having established maximum blood flow in his apparatus, he applied the suction pressure machine to the limb. During the negative phase of the cycle a definite decrease in the arterial inflow and venous output was noted. In the limbs of 3 persons, however, immediately after the negative phase of the cycle had begun there was a slight increase in the arterial inflow, whereas immediately after positive pressure was applied, the outflow from the venous side was increased. He devised an apparatus containing a series of blood pressure cuffs which tended to milk the blood into the leg. The highest cuff was inflated to a pressure of 40 mm of mercury, and each distal cuff was inflated to pressures below this level. The system was inflated and deflated every six minutes. Experimentally he found this machine superior to those of the pavaex type. Heat up to 40 C increased the flow about 8 per cent in normal extremities but very little in diseased extremities. Iontophoresis produced a similar response. The effect of this apparatus on local occlusion was studied. The increase in flow depended mainly on the location and amount of collateral circulation. Obstructions below the knee had less influence on total blood supply than those above the knee.

From these experimental studies, substantiated by clinical studies in association with Smith,⁹⁴ he believed that three principals should be observed in the therapy of occlusive arterial diseases: (1) maintenance of high venous pressure, (2) dehydration of diseased capillaries to facilitate an easy blood flow and (3) when necessary, stimulation of the heart and arterial side by hyperpyrexia or by milder means. They obtained encouraging results using the multiple cuff apparatus on 23 persons with occlusive vascular disease. This group was made up of patients with arteriosclerosis and thromboangitis obliterans. In addition, intra-arterial injections of hypertonic saline solution were given twice weekly. Alcohol in the form of highballs was given to those with arteriosclerosis.

94 Kountz, W. B., and Smith, J. R. Observations on Passive Vascular Exercise and Other Forms of Treatment of Peripheral Vascular Disease, *Am Heart J* 16:55 (July) 1939.

The patients suffering from thromboangitis obliterans received intravenous injections of typhoid vaccine. It was unfortunate from the clinical standpoint that many types of therapy were used in conjunction with one another, thus making the evaluation of each type difficult.

Paine and Levitt,⁹⁵ in a preliminary study, reported favorable results in the treatment of patients with acute and chronic thrombophlebitis by means of intermittent venous occlusion. In 11 unselected patients relief of pain, tenderness and discomfort was obtained. In some cases edema was decreased.

Barker and Counseller⁹⁶ advocated absolute rest in bed, application of moist heat and elevation for postoperative femoral and iliac thrombophlebitis. This therapy was continued for ten to eighteen days, until all evidence of active infection subsided. At this time the patient was advised to walk about with a supporting bandage, preferably of pure rubber, for as long a time as the edema persisted. In a group of 54 patients this routine was adhered to, and 77 per cent of them were able to discard the bandage within three months to a year. At that time no evidence of chronic venous insufficiency had developed. Thirteen per cent were not able to discard the bandage because of slight edema, but in none did marked edema, cellulitis or ulceration develop. In a control group of patients, after a similar length of time only 10 per cent were free from symptoms, 52 per cent presented evidence of venous insufficiency, and 38 per cent had developed severe venous insufficiency with marked swelling, cellulitis and ulceration. A postphlebotic neurosis was present in 12 per cent.

ARTERIAL HYPERTENSION

By DR SCUPHAM AND DR VAN DELLEN

While there have been no outstanding discoveries during the past year in regard to hypertension, the impression is gained that opinion about this disorder is crystallizing into definite form. Hypertension is no longer to be considered a disease but a symptom complex. While it must be admitted that perhaps the majority of patients with hypertension encountered fall into the group with so-called essential hypertension, each patient who presents himself with hypertension must be looked on from the point of view of etiology. The endocrine, renal and organic vascular

95 Paine, J. R., and Levitt, G. The Treatment of Thrombophlebitis of the Deep Veins of the Lower Extremities with Intermittent Venous Occlusion, *Surgery* 5:707 (May) 1939.

96 Barker, N. W., and Counseller, V. S. Treatment of Postoperative Thrombophlebitis, *Proc. Staff Meet., Mayo Clin.* 13:785 (Dec. 14) 1938.

types of hypertension are definite and distinct etiologic types. A good classification was presented by Scott⁹⁷

Renal	Nonrenal
1 Essential hypertension	1 Endocrine disturbances
2 Primary renal disease	(a) Basophilic adenoma of the pituitary
(a) Glomerular nephritis (acute and chronic)	(b) Adrenal tumor
(b) Pyelonephritis	(c) Hyperthyroidism
(c) Urinary obstruction	(d) Menopause
(d) Periarteritis nodosa of renal vessels	(e) Obesity
(e) Polycystic renal disease	2 Vasomotor disorders
(f) Severe amyloidosis of kidney	(a) Increased intracranial pressure
3 Coarctation of the aorta?	(b) Psychic disturbances
4 Eclampsia?	(c) Circulatory failure
	(d) Complete heart block

Wright, Schneider and Ungerleider⁹⁸ called attention to a subject of which most clinicians are cognizant. There are a great deal of variation in the technic of determining blood pressure and a great deal of variation in readings due to differences in perception by persons using the same technic. This lack of uniformity in methods of observation is of great importance, and while it is obvious that personal variations cannot be controlled, it is apparent that there should be uniformity in technic at least. In the returns from a questionnaire sent to medical schools, life insurance companies and individuals, including interns, attending staff members and graduate students, extraordinary variations in technic and observation were encountered. This lack of uniformity is to be deplored, and the writers suggested that this is a subject for study by a national committee.

Scott⁹⁷ in a discussion of the renal origin of hypertension considered the evidence for and against this concept and concluded that the evidence, much of it old, all points to the view that essential hypertension is of renal origin when viewed in the light of the experimental hypertension of Goldblatt.

There can be no question in regard to the relationship of at least certain forms of hypertension to renal disease. Hypertension in association with chronic nephritis, pyelonephritis, obstruction of the lower urinary tract or polycystic kidneys is definitely accepted as being of renal origin. That in most instances so-called essential hypertension is of renal origin has been asserted by several writers and questioned by others.

97 Scott, R. W. Hypertension a Century After Bright, *J. A. M. A.* **111** 2460 (Dec. 31) 1938.

98 Wright, T. S., Schneider, R. F., and Ungerleider, H. E. Factors of Error in Blood Pressure Reading, *Am. Heart J.* **16** 649 (Oct.) 1938.

Scott divided clinical hypertension into renal and nonrenal types. He classified primary, or essential, hypertension as a renal type. He stated further that it now appears that the clinical course pursued in hypertension is determined primarily by the vascular disease in the kidneys. The progress and extent of the vascular disease in the kidneys determine whether essential hypertension runs a benign or a malignant course. Sclerosis of the renal arteries and arterioles in his opinion leads to the renal ischemia. A humoral mechanism produces an increased muscular tone in the peripheral arterioles, which results in an increase in arterial blood pressure. The fact that many patients with hypertension have no evidence of impairment of renal function does not indicate that the hypertension is not of renal origin. He considered the hypertension associated with coarctation of the aorta as due to the ischemia which results from constriction of the aorta above the kidneys.

With this Rytand⁹⁹ was in agreement. He inferred that the increased peripheral blood pressure is on the basis of the impaired renal blood supply. This view is supported by the production of hypertension in rats by partial occlusion of the aorta proximal to at least one renal artery. Hypertension under these conditions Rytand asserted occurs only when there is living renal tissue distal to the point of partial occlusion. Occlusion after nephrectomy never results in hypertension, and hypertension disappears after nephrectomy even though the degree of mechanical obstruction is the same as that necessary to produce hypertension when renal tissue is intact.

The views of Scott are shared to some extent by Dicker,¹⁰⁰ who stated that diminution of the flow of blood to one or both kidneys may induce hypertension of long duration without renal insufficiency. This he also held to be of humoral origin. Thickening of the vessel walls, such as is seen in hypertension in man, he observed in dogs in which hypertension had been present for a considerable period. These animals did not show renal insufficiency. The arteriolonecrosis which occurs in malignant nephrosclerosis results in rapid development of renal insufficiency in the course of hypertension. He expressed the opinion that this process is the result of a more severe grade of vascular ischemia and at the same time results in renal insufficiency. It is primarily a vascular disease process.

Page¹⁰¹ also pointed out, in discussing malignant hypertension, that the function of the kidneys may be but little impaired until late in the

99 Rytand, D. A. The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, *J. Clin. Investigation* **17**:391, 1938.

100 Dicker, E. Benign and Malignant Hypertension, *Bruxelles-med* **19**:323 (Jan.) 1939.

101 Page, I. H. Clinical Study of Malignant Hypertension, *Ann. Int. Med.* **12**:978 (Jan.) 1939.

course of the disease, while the vascular disturbances may be particularly outstanding, especially those in the vessels of the fundi. He noted that often the conduct and emotional stability of patients with malignant hypertension is quite in contrast to the emotional instability sometimes seen in patients with so-called benign essential hypertension.

PATHOGENESIS

Wiggers¹⁰² in a discussion of the dynamics of hypertension was in essential agreement in regard to the similarity between experimental hypertension and essential hypertension in man. He stated that hypertension may be produced experimentally by intracisternal injection of kaolin, by section of the moderator nerves, by damage to the kidneys by ligation of the ureters and by permanent constriction of the renal arteries. It is only the last procedure which is entirely certain to result in increased systolic and diastolic pressures. He stated "A candid evaluation of the reported evidence inclines one to the belief that essential and renal hypertension in man are likewise basically due to unknown humoral agents, but that, as in transient hypertension of normal individuals, vasoconstriction of nervous origin may be superimposed periodically or permanently." He expressed the belief that failure of the moderator nerves cannot be responsible for the nervous factor. The experimental hypertension produced by section of the moderator nerves does not resemble human hypertension, whereas that of renal ischemia essentially does. He discussed the nature of peripheral resistance according to the concepts of central collective and effective peripheral resistance. The latter is the net resistance offered by all the arterioles collectively. The capillary and the venous resistance are of little or no importance as factors affecting central resistance during hypertension. In order to produce peripheral resistance sufficient to cause elevation in blood pressure such as that found in essential hypertension, there must be intensive narrowing of the small vessels in the splanchnic area. Organic lesions of these vessels are not sufficiently widely distributed to be effective. Functional constriction of the arterioles and prearterioles seems to be the essential factor. Wiggers advanced the hypothesis that both in experimental and in human hypertension the functional constriction is not limited to the arterioles but pertains to the entire arterial tree, with constriction of all the muscular elements. This in the smaller arteries accounts for increased peripheral resistance, while in the larger vessels capacity and extensibility are reduced. This would account for the lengthening of pulse pressure which occurs in all cases of hypertension. Diminished elasticity of the aorta and its

¹⁰² Wiggers, C. J. The Dynamics of Hypertension, *Am Heart J* **16** 515 (Nov.) 1938.

larger branches results in increased elevation of the systolic pressure and some lowering of the diastolic. It certainly occurs in atherosclerosis but probably occurs to some extent also when there is little or no sclerotic change in the vessels.

Pickering¹⁰³ in a theoretic discussion of high blood pressure in man agreed essentially as to the relationship between chemical and nervous factors and the cause of hypertension. He was inclined to believe that all areas are subject to arteriolar constriction and essentially to the same degree. He expressed the opinion that local arterial spasm such as has been thought to occur in hypertensive encephalopathy cannot occur. In his discussion he stated the belief that there is unanimity in regard to the presence of functional vasoconstriction as the essential cause of the disorder. That this is of humoral or chemical origin in its essential details seems to be supported by the weight of the evidence which Pickering advanced. The absence of a demonstrable pressor substance in hypertensive persons is a disturbing consideration. It can be explained only on the basis that the pressor substance is fixed immediately in the vessels or that it is present in very minute quantities.

Katz and Leiter¹⁰⁴ correlated the physiologic and clinical features of essential hypertension. They found most writers in agreement in regard to the relationship of increased peripheral resistance to increased arterial pressure and stated that they were essentially in accord with the advocates of this view except that they believed that the nervous control of the peripheral vessels is perhaps more important than the physical and chemical influences which control the peripheral arterioles. The peripheral resistance may be mediated locally in the arterioles by way of an axon reflex or through the peripheral autonomic ganglions, the dorsal root ganglions or the sympathetic and parasympathetic systems in general. Correlating such effective pathways are the vasomotor nerve centers of the spinal cord, medulla and higher centers of the brain. Both humoral and nervous impulses may be effective in initiating responses in these centers. Impulses arrive along the afferent nerves from the special sense organs, viscera and cardiovascular structures themselves. These may be mediated by any part of the cardiovascular system because, according to Katz and Leiter, the vascular end organs are not limited to the carotid arteries and the aorta but are found rather widely distributed in the large vessels. The most important end organs are those located in the carotid sinus. These and the associated nerve supply constitute the moderator mechanism and play a most important part in normal control of blood pressure. Hyper-

103 Pickering, G. W. The Problem of High Blood Pressure in Man, *Proc Staff Meet., Mayo Clin* **14** 310 (May 17) 1939.

104 Katz, L. M., and Leiter, L. Present Conception of Hypertension, *Psychosom Med* **1** 101 (Jan) 1939.

tension may result from one of two types of causes, either an abnormal moderator mechanism, with loss of ability to control the effects of ordinary stimulation, or a normal moderator mechanism subjected to successive stresses exceeding the ability of this mechanism to cope with them. It is stated that an inherent weakness of this mechanism is its ineffectiveness in response to a chronic, persistent elevation of pressure. An abrupt transitory stimulus to the moderator end organs is much more effective. In the presence of arteriosclerosis and the diminution of distensibility of the vessel walls which results, the response may be much reduced. There is no evidence to indicate that the moderator mechanism is defective in hypertension, but it seems likely that in this disease it is exposed to excessive strain which is beyond its capacity to control. The authors agreed that all types of hypertension may be viewed as the result of a disproportion between strain on the moderator mechanism and its ability to cope with such stresses.

They likewise agreed that it does not seem probable that there are any changes in the fundamental hemodynamics of the circulation. All parts of the arterial system are involved more or less to the same degree.

Errors in classifying elevations of blood pressure are to be avoided, and those types of increased pressure secondary to arteriosclerosis, hyperthyroidism and other conditions with high systolic and low or normal diastolic pressures must be eliminated to justify the diagnosis of essential hypertension.

In discussing the mechanism of essential hypertension these writers pointed out that changes in diameter of the small peripheral vessels may easily be overlooked on microscopic examination and that very minute changes may have a profound influence on the blood pressure. Relatively small, superficially not apparent changes in tone of the smooth muscle of many peripheral vessels may result in a sufficient increase in peripheral resistance to produce and maintain an elevation of blood pressure. It is necessary that the peripheral vascular narrowing be universally distributed to maintain hypertension. Neurogenic strains on the moderator mechanism may be brought about by excessive stimulation of the vasomotor apparatus arriving from the sensorium and higher centers of the brain. Hyperactivity of the vasomotor centers brought about by disease or disturbances in the blood supply to the centers may result in increased stimulation of the moderator mechanism. Hyperactivity of the effective mechanism in the myoneural junctions of the smooth muscle of the peripheral blood vessels may exist, but there is no direct evidence to support the view that such increased neurogenic stimulation is constant or complete. Hypertension may be produced by a third method, namely, strains on the moderator mechanism of humoral origin, such as that observed in hyper-

plasia or tumor of the adrenal cortex. However, there is no evidence to prove that the substances arising from the hypophysis or from the adrenal cortex or from the kidney which produce sustained elevation of blood pressure are mediated by this mechanism. The authors stated that the assertion that there is a causal connection between impairment of renal blood supply and high blood pressure cannot be refuted. If this impairment is not primarily of an arteriosclerotic or other organic cause, it must be on the basis of functional renal vasoconstriction. How this vasoconstriction arises and how it mediates the development of hypertension are still unknown. There is at present no way of demonstrating the presence of renal vasoconstriction early in hypertension.

Weiss¹⁰⁵ in his recent review quoted freely from the review of Sodeman, but he expressed the opinion that hypertension is a constitutional disorder in which both hereditary vasospastic and environmental factors are of considerable importance.

Alexander¹⁰⁶ stated that a definite correlation can be found between emotional tensions and fluctuations of blood pressure. In the observation of a patient suffering from chronic mental depression and essential hypertension it was found that when the patient was in an exceptionally calm mental state his blood pressure was somewhat lower and showed smaller fluctuations, with a downward tendency of the average level of blood pressure during the period of treatment. A psychologic reaction in patients with hypertension is generally admitted, and a general hypertensive type of personality has been suggested. Observations on psychic factors in hypertension have been recorded by several other writers (Miller,¹⁰⁷ Saul¹⁰⁸). It seems reasonable to believe that such variations in blood pressure as these authors described are only those noted in normal persons and probably are not related to the genesis of hypertension.

In reporting observations on a group of patients with hypertension, Emerson and Irving¹⁰⁹ stated that "being above the ideal weight" was apparently associated with hypertension. They indicated that the by-products of the incomplete metabolism that accompanies habitual overeating were more likely to be factors in the elevation of blood

105 Weiss, E. Recent Advances in Pathogenesis and Treatment of Hypertension. A Review, *Psychosom Med* **1** 180 (Jan) 1939.

106 Alexander, F. Psychoanalytic Study of a Case of Essential Hypertension, *Psychosom Med* **1** 173 (Jan) 1939.

107 Miller, M. L. Blood Pressure Findings in Relation to Inhibited Aggressions in Psychotics, *Psychosom Med* **1** 162 (Jan) 1939.

108 Saul, L. J. Hostility in Cases of Hypertension, *Psychosom Med* **1** 153 (Jan) 1939.

109 Emerson, W. R. P., and Irving, J. G. Hypertension and Health Diagnosis. Study of One Hundred Cases, *J A M A* **111** 1174 (Sept 24) 1938.

pressure than the increase in weight itself. They stated that the chief cause of hypertension in a group of patients who were not overweight was found in their faulty habits in regard to eating. Most of the patients discussed showed rather moderate increases in blood pressure and probably did not have true essential hypertension. Apparently systolic pressures only were considered, and while observations on systolic pressures may be of some importance in examinations with regard to health, there is apparently little reason to consider them from the point of view of hypertension. The increases in pressure observed were in many instances but little above the average normal for systolic pressure. By continued treatment with control of diet and correction of faulty habits the pressures of the patients under observation apparently fell to lower levels. The authors concluded that in their experience hypertension is a symptom which is frequently the result of faulty health habits rather than the result of physical defects. It is probable that patients with essential hypertension subjected to such measures would show variations in pressure, but it is very unlikely that the diastolic pressure could be reduced to normal or that it would remain normal.

It is interesting to note that Hines¹¹⁰ has been able to observe blood pressure determinations on 1,185 persons from ten to twenty years after initial readings. In the great majority of those with elevation of blood pressure on the original readings hypertension had subsequently developed, whereas only a very small percentage of those who had relatively normal readings originally had acquired hypertension in the interval. He expressed the opinion that this is an indication that instability of blood pressure is a precursor of hypertension.

Engle and Binger¹¹¹ reported on the effect of acetylbetamethylcholine injected subcutaneously into normal and into hypertensive subjects. It was found that in the normal persons there was no significant fall in arterial pressure, while significant decreases occurred in almost every one of the hypertensive subjects. When this experiment was repeated on normal dogs and dogs with experimental renal hypertension, no differences were apparent. This seemed to indicate that the usual type of essential hypertension in man is of a different type from that of renal ischemia.

The writers suggested as a hypothesis that a deficient acetylcholine vasodilator mechanism may be a factor in the production of the arterial hypertension of man.

110 Hines, E. A. The Prognostic Significance of Hyperreactibility of the Blood Pressure in Normal Subjects, *J. A. M. A.* **112** 1016 (March 11) 1939.

111 Engle, D. E., and Binger, M. W. The Blood Pressure Response of Hypertensive Patients to Acetyl-Beta-Methylcholine, *Proc. Staff Meet., Mayo Clin.* **14** 341 (May 31) 1939.

Keith, Wagener and Barker¹¹² in a study of a large group of cases of hypertension found that these cases could be placed in a definite classification according to the degree of severity of the disease and its clinical course. In the cases placed in group I the condition was symptomatic and without impairment of cardiac or renal functions. Age was not a factor, and biopsy of the pectoral muscle showed little alteration in the thickness of the walls. Group II consisted of cases in which the increase in pressure was more sustained. The retinal arterioles showed more changes than were observed in group I, but there was no retinitis. The cardiac and renal functions were likewise not impaired. More frequent arteriolar changes were noted in the muscles. In group III the disease was more severe. The pressure was high and sustained. The peripheral arteries were thick and easily palpable. The cardiac and renal functions were somewhat impaired. Cerebral symptoms were frequent. Angiospastic retinitis was more common, but edema of the disk was not present. Often marked changes were found on biopsy of the arterioles of the muscles. The prognosis was serious. In group IV the condition was grave. Cerebral, cardiac and renal symptoms were often marked. The fundi showed marked angiospastic retinitis. Severe headaches, pains in the muscles and gross hematuria were outstanding symptoms. Biopsy of the pectoral muscle showed variable degrees of change. A progressive angiospastic mechanism seemed to be the outstanding feature.

Heymans¹¹³ reviewed the methods of production of experimental hypertension. In addition to section of the cardioaortic and carotid sinus moderator nerves, injection of kaolin into the cerebral ventricles and production of renal ischemia, another method is the administration of very large doses of vitamin D to dogs. This produces progressive increase in arterial blood pressure with development of arteriolar lesions characterized by necrosis of the endothelium, observed particularly in the kidney but present also elsewhere.

By producing constriction of the renal artery Wilson and Pickering¹¹⁴ were able to produce acute arterial lesions in rabbits which in many were structurally identical with those of malignant hypertension. The degree of hypertension seemed to be the essential factor. The greatly raised intra-arterial pressure seemed to be the chief determinant

112 Keith, N. M., Wagener, H. P., and Barker, N. W. Some Different Types of Essential Hypertension. Their Course and Prognosis, *Am J M Sc* **19** 331, 1939.

113 Heymans, C. Experimental Arterial Hypertension, *New England J Med* **219** 154 (Aug 4) 1938.

114 Wilson, C., and Pickering, G. W. Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, *Clin Sc* **3** 343, 1938.

of these lesions. The defects were particularly severe in the viscera except that there were no defects in the kidney the artery of which had been constricted.

In addition to other methods for the production of hypertension, Nowak and Walker¹¹⁵ reported that ligation of the arteries to the brain producing cerebral ischemia led to hypertension. Such ligation must be carefully done.

Fatherree and Hines¹¹⁶ observed the blood pressure response to epinephrine administered intravenously to patients with normal blood pressure and to others with hypertension. Their observations corroborated those of other workers. The effect of epinephrine on patients with hypertension is essentially no different from that on normal persons. Furthermore, relatively little change in diastolic pressure was noted.

Holman and Page¹¹⁷ in studying the mechanism of experimental hypertension in dogs found the cardiac output to be unchanged both before and after the production of hypertension by constriction of the renal arteries.

Heumans'¹¹⁸ studies on the hypertension produced in dogs by the induction of renal ischemia suggested that the humoral factor increases the excitability of the peripheral blood vessels to vasomotor constrictor stimuli. Peripheral vasoconstriction occurs as well as a disturbance in the physiologic mechanism which normally regulates blood pressure.

Glenn, Child and Page¹¹⁹ demonstrated that there is no definite relationship between the central nervous system and the maintenance of hypertension induced by renal ischemia. In a series of animals in which hypertension had been produced destruction of the spinal cord was followed by a sharp fall in blood pressure, which subsequently rose to a level above that of normal for the animal but not to the previous maximal levels.

Hessel¹²⁰ made some careful studies of the physical and chemical reactions of renin (a kidney extract). He found definite differences in action between this and other pressor substances as far as action

115 Nowak, S J G, and Walker, I J. Experimental Studies Concerning the Nature of Hypertension, *New England J Med* **220** 269 (Feb 16) 1939

116 Fatherree, T J, and Hines, E A, Jr. The Blood Pressure Response to Epinephrine Administered Intravenously to Subjects with Normal Blood Pressure and to Patients with Essential Hypertension, *Am Heart J* **16** 66, 1938

117 Holman, D V, and Page, I H. The Cardiac Output in Arterial Hypertension, *Am Heart J* **16** 321 (Sept) 1938

118 Heumans, C. Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension, *Surgery* **4** 487, 1938

119 Glenn, F, Child, C G, and Page, I. Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs, *Am J Physiol* **122** 506, 1938

120 Hessel, G. Concerning Renin, *Klin Wchnschr* **17** 843, 1938

on smooth muscle is concerned. He observed continuous hypertension in rabbits as a result of daily injections of renin over a period of five weeks. This hypertension persisted for as long as seven months after the injections were discontinued. He was also able to demonstrate the presence of a pressor substance in blood obtained from a renal vein of a dog in which this vein previously had been clamped. These findings may have considerable significance.

The action of renin seems to be directly on the vascular tree. A rise in pressure was observed by Merrill, Williams and Harrison^{121a}. The pressor response was not altered by removing the kidneys immediately before the injection, but a greater rise was obtained if nephrectomy was done two or three days prior to removal of these organs.

Tyramine, as well as renin,^{121b} causes a rise in blood pressure in dogs and rats, with diminution of blood flow and shrinkage of the kidneys and little or no change in renal volume. Renin was found to cause a decrease in renal blood flow, swelling of the kidneys and an increase in the output of urine.

Grossman and Williams^{121d} found that the kidneys of young rats had a higher content of renin than the kidneys of older ones, but the aged animals showed a more marked pressor response to renin.

Major¹²² continued his observations on the presence of guanidine or a similar substance in the blood of persons with hypertension and again expressed the belief that there is present in their blood a greater amount of some such substance than is present in the blood of normal persons.

Katz and his associates¹²³ made long-continued observations on the hypertension produced by renal ischemia in dogs. They corroborated the observations of Goldblatt and others. There are several points of particular interest in their work. They found that variability in the duration of hypertension was not completely dependent on degree of occlusion alone but in part on functional integrity of the other kidney. The way in which this effect is brought about is uncertain. The hypertension is increased and prolonged if the second kidney is removed.

121 (a) Merrill, A., Williams, J. R., Jr., and Harrison, T. R. The Site of Action of the Renal Pressor Substance, *Am J M Sc* **196** 23 (July) 1938, (b) The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Dogs and Rats, *ibid* **196** 240 (Aug.) 1938. (c) Williams, J. R., Jr., Wegria, R., and Harrison, T. R. Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, *Arch Int Med* **62** 805 (Nov.) 1938. (d) Grossman, E. B., and Williams, J. R., Jr. Relation of Age to Renal Pressor Substance, *ibid* **62** 799 (Nov.) 1938.

122 Major, R. H. Blood "Guanidine" in Arterial Hypertension. A Review of Eight Hundred Cases, *Arch Int Med* **62** 946 (Dec.) 1938.

123 Katz, L. N., Friedman, M., Rodbard, S., and Weinstein, W. Observations on the Genesis of Renal Hypertension. *Am Heart J* **17** 334 (March) 1939.

Under these conditions uremia may develop. They found that bilateral and sometimes unilateral nephrectomy was followed by transitory hypertension which they considered to be of neurogenic origin. Interesting, cross transfusion experiments of eighteen hours or more were carried on between dogs having persistent renal hypertension and bilaterally nephrectomized animals. No rise in blood pressure occurred in any of the nephrectomized dogs, indicating the absence of a pressor substance in the blood or its presence in extremely small quantities or perhaps its marked lability. The perfusion of heparinized blood in large quantities from an anesthetized dog with renal hypertension into an isolated denervated hindlimb preparation failed to show the presence of any pressor substance.

Hoerner, Fontaine and Mandel¹²⁴ studied the effect of experimental hypertension of nonrenal origin on the kidneys of dogs. They induced hypertension by section of the moderator nerves of the carotid sinus and the aortic depressors according to the method of Heymans. They found that they could produce by this method a permanent form of hypertension. Eighteen to twenty-four months later they tested the renal function of these dogs and found no clinical evidence of impairment. They then performed unilateral nephrectomy, and histologic examination of these kidneys failed to show any lesion which could be attributed to hypertension.

Prinzmetal, Friedman and Abramson¹²⁵ obtained saline extracts of ischemic kidneys and found that greater pressor effects followed the use of these extracts than that of extracts of the contralateral control kidneys. Similar extracts of spleen and muscle exhibited no pressor qualities. Saline extracts of the kidneys of 21 patients with hypertension produced more definite pressor effects than extracts of the kidneys of persons who had normal blood pressures.

Cross transfusion experiments made by Friedman and Prinzmetal¹²⁶ on patients with malignant hypertension and normal persons failed to show any evidence of significant change in blood pressure. Blood plasma from a patient who had an adrenal pheochromocytoma had a marked effect when injected into the ear vein of a rabbit.

Rabbits' ears perfused with plasma from patients with hypertension revealed no pressor effect, nor did blood or plasma obtained from dogs with renal ischemia. In fact, a depressor effect was sometimes noted

124 Hoerner, G., Fontaine, R., and Mandel, P. Permanent Arterial Hypertension Obtained by Section of Regulators of Pressure and Its Action on Kidney, *Arch. mal. du cœur* **31** 1079 (Nov.) 1938.

125 Prinzmetal, M., Friedman, B., and Abramson, D. I. The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, *Ann. Int. Med.* **12** 1604, 1939.

126 Friedman, B., and Prinzmetal, M. Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension, *Ann. Int. Med.* **12** 1617, 1939.

ENDOCRINE TYPES OF HYPERTENSION

Hypertension, both of the paroxysmal and of the persistent type, in association with disease of the adrenal glands had been reported previously by Nuzum and Dalton. They have now reported 2 additional cases¹²⁷. One of the patients, 62 years of age, became decompensated with low blood pressure. Subsequently hypertension gradually developed over a period of a month. The increased pressure was maintained for several months, until death. At autopsy there was marked hyperplasia of the adrenal cortex as well as cortical adenoma. The second patient presented a picture fairly typical of chronic pheochromocytoma. The authors discussed and reviewed the previously reported cases of hypertension associated with adrenal tumor or disease.

Similar cases are being reported with increasing frequency as the clinical syndrome becomes better known and the condition is considered by clinicians (Brunschwig, Humphreys and Roome,¹²⁸ Palmer and Castlemen)¹²⁹.

Bisgard,¹³⁰ studying a group of patients with hyperthyroidism, found two types of associated hypertension. In these patients the blood pressure was usually significantly elevated above that which might be expected on the basis of hyperthyroidism alone. In some of the patients the elevation in blood pressure was not influenced by thyroidectomy, although symptomatic relief occurred. The blood pressure, both systolic and diastolic, remained high. In a second group, after thyroidectomy both systolic and diastolic pressures receded to a lower level, either normal or nearly normal, where it usually remained, in some of the patients there was a subsequent rise. There was an abnormal response to the cold pressor test in these patients, as well. Bisgard expressed the belief that the relationship of hyperthyroidism to hypertension in such patients is merely provocative, that hyperthyroidism merely exaggerates or precipitates latent hypertension. No relationship was found between the height of the maximal arterial blood pressure and basal metabolism.¹³¹

127 Nuzum, F. R., and Dalton, J. W. Paroxysmal and Persistent Hypertension in Association with Lesions of the Adrenal Glands, *Am Heart J* **16** 643 (Dec) 1938.

128 Brunschwig, A., Humphreys, E. and Roome, N. Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, *Surgery* **4** 361, 1938.

129 Palmer, R. S., and Castlemen, B. Paraganglioma (Chromaffinoma, Pheochromocytoma) of Adrenal Gland Simulating Malignant Hypertension. Report of Case, *New England J Med* **219** 793, 1938.

130 Bisgard, J. D. Relation of Hyperthyroidism to Hypertension, *Arch Int Med* **63** 497 (March) 1939.

131 Reznitskaya, E. Y., and Spivak, P. Y. Basal Metabolism in Hypertension, *Klin med* **16** 1410, 1938.

Van Bogaert and van Baarle¹³² studied the relationship of hypertension to the hypophysis. They examined the spinal fluid of 19 patients and found no evidence of the presence of estrogenic substances except in the fluid from a patient with eclampsia who presented obesity and hypertrichosis. They concluded that there was no direct cause and effect relationship between hypertension and hypophysial disease.

Kylin and von Koranyi¹³³ expressed the belief that the theory of the pituitary origin of hypertension and diabetes has been strengthened as a result of their observations on rabbits into which pituitary glands were transplanted. They found a rise in blood pressure in such animals. The blood pressure fell after a period of several months only to rise again to rather high levels after an interval of six months.

Blood Pressure-Raising Reflexes—Of the blood pressure-raising reflexes, the one most frequently studied and best known is the cold pressor test of Hines and Brown. Recently Hines¹³⁴ called attention to the fact that various investigators using this test have varied the technic and have yet used the criteria of Hines and Brown for interpreting the results. Hines expressed the opinion that any significant change in technic should be attended by the establishment of a new set of standards. He held that the technic is being incorrectly applied, and as a consequence variations in results are being reported. Hines listed certain precautions to be observed in carrying out the test. The subject should be lying down. If other positions are used the effect of posture should be considered. Apprehension on the part of the subject should be prevented by a careful explanation of what is to be done. The subject should not have taken sedatives or vasodilator drugs within a period of twenty-four hours. The subject is allowed to rest in a quiet room for twenty to sixty minutes. Several readings of blood pressure are taken until a basal level has been approximated. In the presence of hypertension a longer period of rest may be necessary. The cuff of the sphygmomanometer is applied to one arm, and the opposite hand is immersed to just above the wrist in ice water. The temperature of the bath should be 4 C. With the hand still in the water readings of blood pressure are taken at the end of thirty and sixty seconds. The higher of the two readings obtained while the hand is in the water is taken as an index of the response. As soon as the sixty second reading has been made, the hand is removed from the ice water. Readings are

132 Van Bogaert, A., and van Baarle, F. Hypertension arterielle et hormones hypophysaires vasopressives et gonadotropes, *Acta med. Scandinav.* **96** 56, 1938.

133 Kylin, E., and von Koranyi, A. Studies on Blood Pressure and Blood Sugar in Rabbits into Which Pituitary Glands Were Transplanted, *Klin. Wchnschr.* **17** 668, 1938.

134 Hines, E. A., Jr. Technic of the Cold Pressor Test, *Proc. Staff Meet., Mayo Clin.* **14** 185, 1939.

taken every two minutes until the blood pressure returns to its previous level. The maximal response usually occurs within thirty seconds, and in a normal subject the pressure usually returns to a basal level within two minutes after the hand has been removed from the cold water. The return is often delayed in the presence of established hypertension. The diastolic response is more reliable than the systolic. Both systolic and diastolic readings should be considered. Inasmuch as the test is a measure of vasoconstrictor tone, the diastolic reading alone is not an adequate criterion. According to Hines's observations, a systolic rise of 20 mm of mercury with a diastolic rise of 15 mm or more indicates hyperactivity. A maximal rise of above 140 mm of mercury systolic and 90 mm diastolic is definite evidence of hyperactivity of the vasoconstrictor mechanism.

Hines and Roth¹³⁵ observed the effect of tobacco on the blood pressure as measured by a standard smoking test. A rise in blood pressure was noted in the majority of persons tested. Successive rises resulted after smoking only in subjects who had evidence of inherent hyperactivity of the vascular system as measured by the cold pressor test. They expressed the opinion that these observations should be interpreted as indicating that this is not the result of a known specific stimulus acting on a hyperactive vascular system but is the result of the presence of some substance in tobacco smoke which directly causes vasoconstriction.

Hammer and Schulte¹³⁶ have made observations of the effect on blood pressure of prostatic massage. Among 378 patients, there was an increase in systolic and diastolic pressure in 75 per cent, while in 23 per cent there was a decrease. There was an increase in pulse rate in all. With 50 subjects in whom these results were observed the cold pressor test was also done. The rise in blood pressure observed was greater, as was the increase in pulse rate, following prostatic massage than in the cold pressor test. In a fair proportion of the subjects a hyperresponse occurred following each procedure. This result is similar to that observed following cold and tobacco smoking.

As another type of reflex, Moore and Allen¹³⁷ made some observations on the carotid sinus reflex in hypertension. They found some variation in different groups of hypertensive persons and expressed the belief that elevation of blood pressure may have different mechan-

135 Hines, E. A., Jr., and Roth, G. M. The Effect of Tobacco on the Blood Pressure as Measured by a Standard Smoking Test, *Proc. Staff Meet., Mayo Clin.* **13**: 524 (Aug. 17) 1938.

136 Hammer, H. J., and Schulte, T. L. Changes in Blood Pressure Produced by Prostatic Massage. *J. A. M. A.* **111**: 308 (July 23) 1938.

137 Moore, F. H., and Allen, E. V. Vascular Climes. Carotid Sinus in Hypertension, *Proc. Staff Meet., Mayo Clin.* **13**: 747, 1938.

isms In these groups they found in the presence of hypertension a rough parallelism between the effect of carotid sinus pressure and the effect of the administration of vasodilator and sedative drugs Carotid sinus pressure, therefore, may be used as an additional method for the determination of the liability of blood pressure

The work of Alam and Smirk¹³⁸ concerning the blood pressure-raising reflexes in health and in hypertension is of considerable interest and importance In the past year they continued observations similar to those previously reported An important blood pressure reflex was demonstrated in their work This consists of exercise of the muscles of an extremity performed during arrest of circulation Such a procedure results in a general systemic rise of blood pressure as well as in the production of pain in the exercised muscles The elevation in blood pressure and the pain in the muscles both persist after cessation of the exercise if the circulation to the extremity remains arrested Both results are proportional to the amount of exercise during the ischemia The rise in blood pressure is of reflex origin and occurs before the appearance of pain in the exercised muscles

Various other sensory stimuli for the production of pain were employed Some of these cause much pain but little rise in blood pressure, others cause less pain but produce some increases in systemic pressure Reflex increases of blood pressure were found to be set up by impulses arising from voluntary muscle which failed to cause pain or discomfort Rises in blood pressure in the same person under similar conditions showed no correlation with the amount of pain They concluded that the reflex rise in blood pressure resulting from this procedure is not dependent on the pain produced The effect of these procedures was observed in a patient having a lesion of the spinal cord in whom there was an interruption of the sensory pathway in the affected extremity Exercise of this extremity during the circulatory arrest resulted in no elevation in blood pressure, while in the normal extremity the usual rise occurred It would seem that the authors are correct in concluding that their observations in this case confirm the belief that such increase in blood pressure is the result of a reflex which results from the accumulation of metabolites in the muscles of a normally innervated leg

These investigators studied this reflex in persons with hypertension of the essential type as well as in those having definite renal disease They employed, in addition, the cold pressor test with immersion of

138 Alam, M., and Smirk, F. H. (a) Blood Pressure Raising Reflexes in Health, Essential Hypertension, and Renal Hypertension, *Clin Sc* **3** 259 (Aug) 1938, (b) Unilateral Loss of a Blood Pressure Raising, Pulse Accelerating Reflex from Voluntary Muscle Due to a Lesion of the Spinal Cord, *ibid* **3** 247 (Aug) 1938, (c) Observations in Man Concerning the Effects of Different Types of Sensory Stimulation upon the Blood Pressure, *ibid* **3** 253 (Aug) 1938

two thirds of the forearm and the arrest of circulation. Circulatory arrest during immersion caused the temperature of the arm to fall more rapidly than when the circulation was free, because the degree of cold attained was dependent on the rate of flow of blood through the arm. They pointed out that under the conditions of circulatory arrest the actual stimulus is of constant intensity, and its effectiveness varies according to the sensitivity of the subject to cold. This method was compared with exercise of an ischemic limb. With normal persons both blood pressure-raising reflexes were found to be greater in their effect in old than in young subjects when the systolic blood pressure alone was observed. The rise in diastolic pressure was approximately the same for both age groups. In persons who had chronic nephritis with hypertension the effects on both systolic and diastolic pressures were found to be less than those observed in normal subjects of the same age group. Large rises in pressure were more frequent in the patients with essential hypertension than in normal controls of the same age group. However, large rises were found in a few normal subjects and only small rises occurred in some persons with hypertension. This would indicate that high reactivity to such a blood pressure-raising reflex cannot by itself explain a high level of resting blood pressure. Such a high degree of reactivity may express itself, therefore, in daily life by remarkable variations in blood pressure. This may, perhaps, sometimes lead to permanent hypertension. The writers stressed the fact that the average blood pressure of subjects showing a high degree of reactivity is no greater than the average blood pressure of subjects with a low degree of reactivity. They found the incidence of high reactivity among their patients in an Egyptian hospital practice much greater than the incidence of hypertension.

In normal subjects exercise of an ischemic arm resulted in either no change or slight slowing of the pulse rate. In patients with hypertension the pulse rate usually increased. This is in contrast to what is usually observed. This reversal of the blood pressure-pulse rate relationship in hypertension might be of considerable importance if it could be shown to be due to a change in the reactions of a depressor mechanism.

Thus it would seem that such blood pressure-raising reflexes are to be regarded as indicators of a hyperreactive state of the vasomotor mechanism rather than as an essential part of the mechanism of the production of essential hypertension, unless it may be considered that such a tendency toward vasoconstriction is the precursor of the actual change which results in hypertension. The blood pressure-raising reflex of Alam and Smuk is interpreted by them as being one of the natural defensive mechanisms of the body designed to increase the rate of blood flow through fatigued muscles by raising the general blood pressure.

Normal persons and persons with hypertension were subjected to inhalation of carbon dioxide by Hardgrove, Roth and Brown¹³⁹ The pressor reaction from this procedure was determined in both groups A definite rise in blood pressure was found There were no significant differences in the two classes of persons except that with the application of cold there was a greater rise in pressure in those with hypertension, particularly if the condition was in the early stages In the more advanced stages this rise was less marked Such an observation might be the result of reflex transmission of a peripheral stimulus to a more highly reactive vasomotor center in the hypertensive person Why this should occur is still obscure

Leiter¹⁴⁰ reported 2 unusual cases of renal hypertension One of the patients was a man of 40 who showed a rise of systolic and diastolic pressure Only four months elapsed between the first rise in blood pressure and the patient's death At autopsy extensive atrophy was noted in the kidneys, which apparently was dependent on occlusion of the corresponding arcuate and interlobar arteries The occlusion of these vessels was apparently sufficient to result in ischemia of at least portions of the kidney, and thus the condition appeared to be similar to the Goldblatt type of experimental hypertension The cause of the arterial disease is not clear, although the patient had syphilis In the other patient the analogy to experimental hypertension was still more striking in that the left renal artery was completely occluded by an arteriosclerotic plaque and the right renal artery was markedly narrowed Apparently hypertension in this case had persisted over a long period

Similar cases are being reported with increasing frequency, such as the one described by Blatt and Page,¹⁴¹ in which the renal arteries were constricted by a lymphosarcoma Freeman and Hartley¹⁴² observed a patient with hypertension who had a solitary, ischemic kidney

Schroeder and Steele¹⁴³ found some abnormality of the urinary tract in 50 of 79 patients with hypertension They were able to demonstrate these defects by means of intravenous pyleograms This seems to be an astonishingly high proportion showing renal involvement with

139 Hardgrove, M, Roth, G M, and Brown, G E The Pressor Reaction Produced by Inhalation of Carbon Dioxide Studies of Patients with Normal Blood Pressure and with Hypertension, *Ann Int Med* **12** 483, 1938

140 Leiter, L Unusual Hypertensive Renal Disease Occlusion of Renal Arteries (Goldblatt Hypertension), *Anomalies of Urinary Tract, J A M A* **111** 407 (Aug 6) 1938

141 Blatt, E, and Page, I H Hypertension and Constriction of the Renal Arteries in Man Report of a Case, *Ann Int Med* **12** 1690, 1939

142 Freeman, G, and Hartley, G Jr Hypertension in Patient with Solitary Ischemic Kidney, *J A M A* **111** 1159 (Sept 24) 1938

143 Schroeder, H A, and Steele, J M Abnormalities of Urinary Tract in Essential Hypertension, *Proc Soc Exper Biol & Med* **39** 107, 1938

hypertension No doubt such abnormalities occur with sufficient frequency in association with hypertension to make it necessary that they be considered in every case of this disease

PATHOLOGY OF HYPERTENSION

Many writers have during the past hundred years considered the cause and effect relationship of the arteriolar changes found not only in the renal structures but in the general and systemic arterioles Keith and his co-workers at the Mayo Clinic have been impressed with the relationship of alterations in the structure of the arterioles to hypertension In the past year they continued their pathologic studies of the arterial system in severe hypertension and became convinced that, regardless what the cause of hypertension may be, in the later stages of the disease there are widespread arterial and particularly arteriolar lesions

Odel¹⁴⁴ studied the structural changes in the arterioles of the myocardium in patients with hypertension in the malignant phase These alterations they found to be similar to those described as occurring in the arterioles of the pectoral muscle These changes do not occur with any degree of consistency and are not present in every such patient, and when they are found they are less marked in the myocardium than in other organs of the same person There are also marked variations in the degree of change in different persons, as well as in various vessels of the myocardium of the same person Chronic diffuse fibrosis was found to involve the myocardium of patients with malignant hypertension more commonly than that of patients having less severe types of arterial hypertension

Morlock¹⁴⁵ studied the arterioles of the viscera in similar groups and found a definite increase in thickness of wall and reduction of the ratio of wall to lumen in the arterioles of hypertensive subjects This was severe proportionally to the severity of the hypertension Hyperplasia of the nuclear elements of the media appeared to be an earlier change, while degeneration and fibrosis occurred later The arterioles of the pancreas, liver, gastrointestinal tract and spleen were observed The contrast between these vessels in normal persons from youth to old age and those in hypertensive subjects was definite

Rosenberg¹⁴⁶ reported on the cerebral vessels in patients with malignant hypertension and pointed out that in the brain as elsewhere

144 Odel, H M Arteriolar Changes in the Myocardium in Diffuse Arteriolar Disease with Hypertension, Group IV, Proc Staff Meet, Mayo Clin **14** 210, 1939

145 Morlock, C G Arterioles of the Pancreas, Liver, Gastro-Intestinal Tract and Spleen in Hypertension, Proc Staff Meet, Mayo Clin **14** 214, 1939

146 Rosenberg, E F The Brain in Malignant Hypertension, Proc Staff Meet, Mayo Clin **14** 217, 1939

in the body there is a definite separation of the findings in arteriosclerosis of the larger vessels and the vascular effects of hypertension. Two major pathologic processes which affect the brain of a patient with malignant hypertension are hemorrhage and thrombosis. In some cases small spotty hemorrhagic areas are distributed throughout the brain structure. These are usually associated with small infarctions. In other cases numerous minute capillary hemorrhages occur, often so small as to be seen only on microscopic examination. Such capillary hemorrhages are probably responsible for considerable irritation of the brain. Both large infarctions and multiple miliary infarctions were noted. Edema of the brain and increase in the quantity of intracranial fluid seemed to occur rather frequently. The finding of many small cortical lesions may furnish an explanation of the convulsions noted in many of these cases. Cerebral arterioles were found to be altered markedly in such cases of malignant hypertension. These changes resembled those found in the arterioles of other viscera and consisted of an increase in thickness of wall and a reduction of the ratio of wall to lumen. Cerebral phenomena of malignant hypertension, often designated as the cerebral crises of hypertensive encephalopathy and often ascribed to vasospasm, seem much more likely to be on the basis of such widespread destructive arteriolar or capillary lesions, either infarction or hemorrhage, or both. There is no anatomic evidence that vasospasm occurs. Vasospasm has been observed in the retinal arteries by ophthalmic examination, but in the opinion of Kernohan it does not persist sufficiently long to destroy nerve cells of the retina and impair vision. He likewise thinks that the thickening of the walls of the arterioles cannot be the cause of hypertension. This thickening is to be considered compensatory hypertrophy of the musculature of the media. When the walls have become sufficiently thick that nourishment is diminished, degeneration follows. Necrosis and liquefaction of the media may occur with lesser degrees of impairment of nutrition. Fatty degeneration may occur and minimal amounts of fibrosis develop. Endothelial proliferation is a late occurrence.

Rosenberg, Keith and Wagener¹⁴⁷ reported 2 interesting cases of widespread arterial disease. Both patients showed elevation of blood pressure. Diffuse arterial disease was the cause of death in both. In one the course was rapid and hypertension was sustained. The clinical manifestations were those referable particularly to the central nervous system, retina, heart and kidneys. The phenomena exhibited were on the basis of simultaneous involvement of the arterioles in all these

147 Rosenberg, E. F., Keith, N. M., and Wagener, H. P. Diffuse Arterial Disease with Hypertension. Two Unusual Cases of Contrasting Types, *Arch. Int. Med.* 62:461 (Sept.) 1938.

structures—on the basis of spasm or of acute or chronic pathologic reactions in the majority of the arterioles. Fever and leukocytosis with marked toxemia and inflammatory-like lesions in the small arteries suggested that the disease was one of an infectious or toxic origin involving the arterioles and resulting in severe hypertension. In the second patient the clinical course was very much slower. The hypertension was rather mild, with the development of atherosclerotic lesions in the arteries. The disease picture terminated with the development of thromboses in the vicinity of the atheromatous lesions. The fundamental change in the second patient was that of arteriosclerosis. Hypertension in this patient was relatively mild, without marked increase in diastolic pressure, while in the first patient hypertension was severe and diffuse involvement of the arterioles was the outstanding defect. This is in contrast to Shapiro's case,¹⁴⁸ in which hypertension had been present for more than twenty-five years. At autopsy there were no alterations in the structure of the arterioles of the kidneys.

A CRITICAL REVIEW OF THE SURGICAL TREATMENT OF VASCULAR DISEASES

BY DR DE TAKÁTS AND DR BECK

The literature contains no report of drastic departures from accepted methods of treatment, some of the enthusiasm shown in the reports of previous years is giving way to sober evaluation of the results obtained. The importance of close cooperation between surgical and medical groups and the value of combining physical therapy, drug therapy and operative procedures are becoming more and more obvious.

PARAVERTEBRAL BLOCK

The treatment of patients with apoplexy by infiltration of the stellate ganglion with procaine hydrochloride, as originally conceived by Leriche, was evaluated by Mackey and Scott.¹⁴⁹ In 19 patients stellate infiltration was carried out by the posterior route, and 9 of them showed definite improvement. In 1 patient an inadvertent intravenous injection almost caused death from respiratory failure. In older patients with severe cerebral hemorrhages the method has failed. Patients with cerebral thrombosis may show some improvement. The ideal patient for this type of treatment is a young person with cerebral embolism. The injection should be given as soon as possible after the

148 Shapiro, S. Report of Case of Essential Hypertension of More Than Twenty-Five Years' Duration Showing No Renal Arteriolar Changes at Autopsy, *J Lab & Clin Med* **24** 60, 1938.

149 Mackey, W. A., and Scott, L. D. W. Treatment of Apoplexy by Infiltration of the Stellate Ganglion with Novocain, *Brit M J* **2.1** (July 2) 1938.

onset of apoplexy, as its purpose is to relieve the collateral edema around the vascular occlusion and thereby diminish the extent of residual damage. Only negligible improvement can be expected from treatment begun as late as twenty-four hours after the onset.

In our experience the anterior approach for injecting the stellate ganglion is simpler. If the method is to become useful, it must be taught to the medical residents in hospitals, who can be ready to inject the ganglion on the side of the accident within a short time. Huge intraventricular hemorrhage, with increasing coma and Cheyne-Stokes respiration, will obviously be unaffected, as in 1 patient under our observation, but if intravascular or intraspinal injection is avoided the treatment should do no harm. The dramatic recoveries of some of the patients described by Mackey and Scott stimulate more extensive trial of the method.

In strict analogy with the idea of releasing collateral vasospasm and edema of the brain in cerebral thrombosis is the suggestion of Ochsner and DeBakey,¹⁵⁰ again based on the idea of Leiche, that thrombophlebitis causes edema not only because of venous and lymphatic block but because of a reflex spasm of veins, arterioles and arteries. This vasospasm manifests itself by a decrease in arterial pulsations, cooling of the digits and increased permeability of the vascular endothelium, which in turn leads to an outpouring of fluid high in protein. The authors reported 17 cases in which following one or several injections of procaine hydrochloride to the sympathetic chain a rapid disappearance of pain, fever and edema were observed. The patients got out of bed in a few days and evidence was presented that no residual edema developed, in spite of the fact that no elastic support was prescribed. If this procedure can really prevent the cumbersome and painful thrombophlebitic inductions and ulcerations, it will mean a marked advance in the treatment of thrombophlebitic edema.

It should be pointed out, however, that not all patients show clinical evidence of such reflex spasm of vessels. In fact, some of them exhibit signs of vasodilation. To make paravertebral injections requires a certain amount of study and practice. A successful block of the sympathetic chain should be followed by a rise in the temperature of the skin and a cessation of sweating in the limbs whose sympathetic nerve supply is blocked.

In previous reviews we emphasized the importance of the spasm of collateral vessels when arterial pathways become suddenly obstructed, heat, suction and pressure as well as injections of papaverine hydrochloride have been recommended to overcome this reflex effect. When

¹⁵⁰ Ochsner, E. W. A., and DeBakey, M. Treatment of Thrombophlebitis by Novocain Block of Sympathetics, *Surgery* 5: 491 (April) 1939.

the interval of time for embolectomy has passed, arteriectomy may be proposed¹⁵¹ It might be worth while to add block of the sympathetic pathways to these methods as clearcut experiments have shown the protective effect of sympathectomy following arterial ligations¹⁵²

But the interruption of these vascular reflexes may have more than a temporary effect Elsewhere one of us (G de T) drew attention to a group of reflex dystrophies¹⁵³ in which a reflex is activated by some focus of irritation, such as a thrombus, this reflex does not subside when the original exciting cause disappears but becomes a fixed, self-perpetuating mechanism leading to so-called traumatic edema painful osteoporosis or Sudëck's atrophy It remains to be seen whether early interruption of these reflexes may not prevent the circulatory disturbances which are encountered following vascular accidents Only recently Villaret and Cachera¹⁵⁴ studied the vasomotor phenomena of the brain consecutive to embolism and found that the vasomotor system was greatly disturbed, thus possibly contributing to the late sequelae of cerebral accidents

Severe paroxysmal tachycardia, following appendectomy and leading within a few hours to cardiac failure, was successfully aborted by Leibovici, Dimkin and Wester¹⁵⁵ with an injection of procaine hydrochloride into the left stellate ganglion The pulse promptly fell from 180 to 72, and the blood pressure, which had been gradually falling from 130 mm systolic and 80 mm diastolic to 80 mm systolic and 50 mm diastolic, also returned to normal The 29 year old patient never had another attack, and an electrocardiogram taken a few weeks later showed no aberration from the normal The authors collected 8 cases of sinus tachycardia and 5 cases of paroxysmal tachycardia in which ganglionectomy or injection of procaine hydrochloride was done With the paroxysmal type the block of the sympathetic nerves was less successful than with the former In this particular case, morphine, camphor, ouabain and quinidine were all tried, as well as ocular and carotid sinus compression, without avail, before block of the stellate ganglion was undertaken

151 Griffiths, D L E Arterial Embolism, *Lancet* **2** 1339 (Dec 10) 1938

152 Mulvihill, D A, and Harvey, S C Studies on Collateral Circulation I Thermal Changes After Arterial Ligation and Ganglionectomy, *J Clin Investigation* **10** 423 (Aug) 1931

153 de Takats, G Reflex Dystrophy of the Extremities, *Arch Surg* **34** 939 (May) 1937

154 Villaret, M, and Cachera, R Les répercussions vasculaires tardives de l'embolie cérébrale en pathologie expérimentale, *Presse méd* **47** 267 (Feb 18) 1939

155 Leibovici, R, Dimkin, L, and Wester Accés post-opératoire grave de tachycardie paroxystique traité avec succès par la novocaïnisation du ganglion stellaire gauche, *Presse med* **47** 83 (Jan 18) 1939

PHLEBOTOMY FOR ILIOFEMORAL THROMBOSIS

Kulenkampff ¹⁵⁶ reported 61 cases in which he probed and extracted a thrombus from the femoral vein through an opening in the saphenous. An analysis of his cases shows that in many the operation was premature or unnecessary, as little was found outside of thickened adventitia or periphlebitic exudate. Nevertheless in a well selected case, especially if a pulmonary shower has already occurred, the operation should be seriously considered, as sometimes the second or third embolus proves to be fatal. Our own experience with this method is limited, and more exact indications will have to be worked out in the future. The operation is easily performed, does not necessitate a venous suture and does not result in obstruction of the deep veins. Lawen ¹⁵⁷ approached such a thrombus through an incision of the femoral or iliac vein with temporary proximal occlusion of the vein. This procedure requires a venous suture, and it seems to us that the chances of renewed thrombus formation are thereby greatly increased.

These two procedures undertaken for bland, static thrombi are not comparable to those reported in last year's review ¹⁵⁸ for ligating veins proximal to septic thrombi. These were undertaken to prevent feeding of septic material into the blood stream.

USE OF HEPARIN IN SURGICAL OPERATIONS ON BLOOD VESSELS

Murray and Best ¹⁵⁹ published the far reaching results of their animal experiments, which show that arterial anastomosis, venous graft into an arterial segment and arterial embolectomy can be readily performed without the formation of a thrombus, provided the animal has received sufficient amounts of heparin either in the local vascular segment or in the systemic circulation. According to Murray, embolectomy in man can now be performed even after the lapse of a day, since the reformation of the clot can be prevented by heparin.

Since the advent of the purified product, heparin can be safely administered to the patient intravenously. The ordinary intravenous drip is used, and to the salt solution sufficient heparin is added to increase the clotting time of the blood of the patient to about fifteen minutes. Usually heparin is added in the proportion of 10 units of

156 Kulenkampff, D. Die Verhütung schwerer und tödlicher Embolien durch Ausraumung der Vena iliaca, *Arch f klin Chir* **193** 727, 1938.

157 Lawen, A. Weitere Erfahrungen über operative Thrombenentfernung bei Venenthrombose, *Arch f klin Chir* **193** 723, 1938.

158 Scupham, G. W., de Takats, G., Van Dellen, T. R., and Beck, W. C. Vascular Diseases. A Review of Some of the Recent Literature, with a Critical Review of the Surgical Treatment, *Arch Int Med* **62** 482 (Sept.) 1938.

159 Murray, G. D. W., and Best, C. H. The Use of Heparin in Thrombosis, *Ann Surg* **108** 163 (Aug.) 1938.

heparin to 1 cc of salt solution, in the average patient this solution should run at about 25 to 30 drops a minute

At present the expense of the material and the difficulties encountered in its shipment from Canada restrict the use of this highly significant product. Whether it will have wide application in the prevention and treatment of postoperative thrombosis, pulmonary embolism, coronary thrombosis and cerebral thrombosis is yet to be seen; in suturing of blood vessels, however, the indications for it are so clearcut and striking that its routine use will bring about marked improvement in results. The suturing of aneurysms and the closing of arteries from which emboli have been extracted are greatly facilitated by the use of heparin. This is a most important contribution to vascular surgery.

PROCEDURES FOR THE TREATMENT OF ANEURYSMS

Arteriovenous Aneurysms—Reid and McGuire⁶⁹ analyzed 21 cases of arteriovenous and 9 cases of cirsoid aneurysm, and supplemented their analysis by experimental observations in dogs. In 16 of the cases of arteriovenous aneurysm operation was done, and in all except a case of pulsating exophthalmos the condition was cured. In 2 instances the aneurysm healed spontaneously. In all of the 9 cases of cirsoid aneurysm operation was done, and in 3 the condition was cured and in the other 6 it was more or less improved. There were no deaths in the entire series of 30 cases.

Their physiologic observations have been discussed in a previous part of this review. Extensive clinical observations were presented on cardiac damage, thinning and dilatation of the proximal artery, circulation time, blood volume, the bradycardic phenomenon on closure of the fistula, alterations in blood pressure, venous pressures and the extent of collateral circulation. In addition, there is a wealth of important technical suggestions. Two new methods of dealing with these exceedingly complicated arteriovenous fistulas are presented. In addition, the proper time to operate and the standard curative procedures are discussed.

Not only is this contribution a great source of information to the surgeon, but it emphasizes the extent to which the cardiac damage can be reversed by permanent closure of the fistula. It must be regarded, together with the previous articles of the senior author and those of Halsted, Matas and Holman, as the foundation of all present knowledge on the subject. It also contains a number of interesting data on the physiology of circulation.

Arterial Aneurysms—A subclavian aneurysm producing gangrene of two fingers and caused by a cervical rib was reported in a young

woman in her early twenties¹⁶⁰ Resection of the sac and removal of the supernumerary rib effected a cure In a patient with a similar lesion, but who was much older, one of us (G de T) performed proximal and distal ligation of the artery with scalenotomy We have come to regard a roentgenogram of the cervical spine as an almost routine procedure in any case of arterial obstruction of an upper extremity Oblique views directed upward and medially will show such a rib most clearly The study of 1,000 thoracic roentgenograms of children revealed an incidence of cervical rib in 1.2 per cent¹⁶¹ A cartilaginous connection between the seventh transverse process and the first rib, however, will not be represented in roentgenograms

Popliteal aneurysms are again receiving attention While Kimpton and Sanderson¹⁶² reported successful suture of such an aneurysm with imbrication in 2 cases, Yater¹⁶³ reported that in his cases the aneurysm ruptured and amputation became necessary

Dandy¹⁶⁴ contributed another important article on the treatment of intracranial aneurysms He presented 3 cases of aneurysm of the intracranial portion of the internal carotid artery In each case the aneurysm was alongside the carotid artery as it came through the cavernous sinus In each instance it was treated by trapping it between a proximal ligature—that of the internal carotid artery in the neck—and a distal ligature, placed intracranially, with the help of a silver clip All the patients were symptomatically cured He discusses the importance of arteriography for the localization of these lesions

In studying this article one cannot escape the feeling that the rational treatment of intracranial aneurysms has just begun and great advances are to be expected in the future

SYMPATHETIC GANGLIONECTOMY FOR PERIPHERAL VASCULAR DISEASE

Sunder-Plassmann,¹⁶⁵ well known for his extensive neurohistologic studies on the vegetative nervous system, stained the sympathetic ganglions removed at operations for Raynaud's disease with

160 Baumgartner, A, Clerc, A, and Macrez, C Sur l'aneurysme arteriel de voisinage et la gangrene ischémique des doigts en rapport avec les côtes cervicales Leur traitement chirurgical, *Presse med* **46** 1665, 1938

161 Davis, D B, and King, J C Cervical Rib in Early Life, *Am J Dis Child* **56** 744 (Oct) 1938

162 Kimpton, A R, and Sanderson, E R Popliteal Aneurysm Report of Two Cases, *New England J Med* **220** 146, 1939

163 Yater, W M Rupture of Popliteal Aneurysm, read before the American Heart Association, St Louis, May 13, 1939

164 Dandy, W E The Treatment of Internal Carotid Aneurysms Within the Cavernous Sinus and the Cranial Chamber, *Ann Surg* **109** 689 (May) 1939

165 Sunder-Plassmann, P Die Raynaudsche Erkrankung und ihr Formenkreis, *Deutsche Ztschr f Chir* **251** 125, 1938

Bielschowsky's stain and found definite pathologic changes pointing to toxic damage of the ganglions, fibrils and terminal reticulum. Allergic phenomena may also be at play. He expressed the belief that sympathectomy is not real denervation of the vessels as the terminal nervous network remains and is reactive. This, of course, is the opinion of Stohr, previously reviewed. The author advocated administration of thyroid extract and vitamin B₁ in the postoperative period for improving end results.

The effect of sympathectomy on the vasa vasorum of the rat was reported by Griffith¹⁶⁶. He injected carbon particles into the blood stream and found a greater number of these particles in the sympathectomized vessels, from this he concluded that the nourishment of the vessel wall improves after sympathectomy.

Lewis⁶² reemphasized his belief that the local fault in the vessels of patients suffering from Raynaud's disease is the decisive factor determining end results. He examined 6 unselected patients shortly after preganglionic sympathectomy for Raynaud's disease. In 3 patients attacks occurred spontaneously or could be produced, indicating that local susceptibility to cold remains, the structural damage to the digital vessels seems to determine the failure to abolish all symptoms.

This work of Lewis, together with evidence accumulating elsewhere,¹⁶⁷ is in opposition to the view again strongly expressed by Smithwick¹⁶⁸ that a preganglionic sympathectomy for the upper extremity is the operation of choice for Raynaud's disease. In our experience an extremity in which complete sympathetic denervation has been accomplished, as indicated by cessation of sweating, shows a smaller number of recurrences than the one in which the important first white ramus has been preserved. The controversy regarding preganglionic versus postganglionic sympathectomy still continues and will finally be solved by studying comparable cases over several years.

A highly stimulating study of pain in a fantom limb by Livingston¹⁶⁹ is directed against the often annoying and sometimes permanently intractable pain in an amputated limb projected distally to the level of amputation. He advocated the injection of procaine hydrochloride into the sympathetic ganglions, which curiously enough abolishes this pain for several months or years and may then have to be repeated. The author expressed a doubt that an interruption of afferent sensory fibers

166 Griffith, J. A. The Effect of Sympathectomy on the Vasa Vasorum of the Rat, *Am J Path* **20** 984, 1938.

167 de Takáts, G. Analysis of Results Following Sympathectomy for Peripheral Vascular Disease, *Am J Surg*, to be published.

168 Smithwick, R. H. Immediate Effects and Late Results of Sympathetic Denervation of the Upper Extremity by Preganglionic Section, read before the American Heart Association, St. Louis, May 13, 1939.

169 Livingston, W. K. Fantom Limb Pain, *Arch Surg* **37** 353 (Sept.) 1938.

is accomplished but held that a reflex arc is broken, which may not reestablish itself after the temporary block with procaine. This line of thought is similar to that expressed by our group in regard to "reflex dystrophies" following slight injuries or infections¹⁵³

Lumbosacral sympathectomy was performed on 5 patients suffering from diabetic gangrene¹⁷⁰. The authors expressed the opinion that the operation delayed the process of gangrene, limited the infection and reduced the claudication. How this was brought about and how the patients were selected are not apparent. It is not all clear why a process which is predominantly an obliteration of the middle-sized and terminal arteries would be benefited by sympathectomy. Should a vasopastic element be present, heat and rest in bed would effectively reduce it.

In 6 patients suffering from hyperhidrosis White¹⁷¹ obtained excellent results by preganglionic sympathectomy. Only 1 patient had a paravertebral injection of alcohol, but as such treatment is occasionally followed by intercostal neuritis, the author expressed a preference for surgical removal of the upper thoracic chain with preservation of the first white ramus. Thus Horner's syndrome is avoided.

Our unpublished observations have made us cautious in advocating sympathectomy for hyperhidrosis unless it is strictly limited to the extremities. In 1 patient all the extremities were subjected to sympathectomy, but the sweating in the nondenervated areas became almost unbearable. Psychotherapy, tried in 1 case, resulted in no benefit. Hyperhidrosis without vascular spasm deserves further intensive study.

Telford¹⁷² stated that while the patchy type of scleroderma may be stopped by sympathectomy, the sclerodactylia seen in the late stages of Raynaud's disease is not affected by the operation. In cases of hyperhidrosis the results were excellent. In 27 cases of poliomyelitis and 40 cases of erythrocyanosis, a condition more frequent in England, the results were very good. The author expressed the belief that sympathectomy has a definite place in well selected cases of skin disease.

SURGICAL TREATMENT OF HYPERTENSION

Smithwick¹⁷³ expressed succinctly the present status in this field as follows: "The surgical attack on hypertension must still be regarded

170 Chabanier, H., Gaume, P., and Lobo-Onell, C. De la sympathectomie lombo-sacrée dans les artérites diabétiques des membres inférieurs, *Presse med* **46** 1161 (July 27) 1938.

171 White, J. C. Hyperhidrosis of Nervous Origin and Its Treatment by Sympathectomy, *New England J. Med.* **220** 181, 1939.

172 Telford, E. D. Some Experiences of Sympathectomy in Diseases of the Skin, *Brit. J. Dermat.* **50** 637, 1938.

173 Smithwick, R. H. Surgery of the Sympathetic Nervous System, *New England J. Med.* **220** 475, 1939.

as in the experimental stage. It takes years of trial and error to determine the most effective way of denervating any portion of the vascular bed. The lack of uniformity of results in identical cases leads one to suspect that this has not yet been accomplished in regard to the splanchnic bed."

This statement expresses the quandary in which every surgeon who is familiar with the results of sympathectomies for hypertension finds himself. If he has followed his patients carefully, he has seen a number of objective and a smaller number of subjective failures. He has occasionally seen a remarkable result, perhaps in a patient in whom he least expected it. All the preoperative tests notwithstanding, the results of the surgical procedure are yet unpredictable. That section of the splanchnic nerve or denervation of the adrenal gland does not exert any influence through denervation of the adrenal medulla was pointed out by Hermann,¹⁷⁴ who stated that in the dog the adrenal medulla does not change morphologically nor does it lose its power to secrete its specific hormone or to react to electric or to pharmacologic stimuli. He expressed the opinion that the gland can escape the control of the central nervous system without losing the capacity to produce and discharge epinephrine, this should be taken into account when operations for hypertension or diabetes are under consideration.

Craig¹⁷⁵ restated the indications, preoperative tests and results of subdiaphragmatic section of the splanchnic nerve with reference to 158 patients treated at the Mayo Clinic. All patients are divided into four groups, as discussed elsewhere in this review. The first group requires no surgical treatment, and the second and third groups should be considered for surgical treatment, whereas in the fourth group the findings constitute a contraindication. In general, 70 per cent of the patients operated on were benefited.

C. H. Moore¹⁷⁶ reported on 22 patients in whom section of the splanchnic nerve had been performed and who had been followed up for a period of more than thirty months, 90 per cent of these showed an immediate postoperative drop in blood pressure. The reduction of blood pressure was maintained for over a year in 45 per cent. Symptomatic improvement, without a fall in blood pressure, was noted in 27 per cent. No improvement other than some immediate relief was registered in 27 per cent. In 9 per cent not even an immediate drop was noted. One patient (4 per cent) died.

174 Hermann, H. Le comportement de la glande médulosurrénale énnervée (données expérimentales), *Presse méd* **46** 1554 (Oct 22) 1938.

175 Craig, W. M. Essential Hypertension. Selection of Cases and Results Obtained by Subdiaphragmatic Extensive Sympathectomy, *Surgery* **4** 502 (Oct) 1938.

176 Moore, C. H. Surgical Treatment of Hypertension, *South Surgeon* **7** 353 (Aug) 1938.

Such reports as these are urgently needed. One cannot brush aside these operations with the remark that they constitute a form of psychotherapy. With 72 per cent of the patients showing either a fall in blood pressure or no fall but definite symptomatic improvement, one feels encouraged to continue in spite of many failures.

That exclusion of the splanchnic bed seriously interferes with a reflex pressor mechanism is clearly illustrated by the observations of Moore and Allen,¹⁷⁷ who found that following section of the splanchnic nerve pressure on the carotid sinus results in significant decreases of blood pressure associated with marked bradycardia. Just how long this sensitivity of the carotid sinus persists is not clear. It is known that the postural hypotension resulting from this operation is temporary.

The work of Goldblatt on experimental renal hypertension is beginning to exert its influence on the clinical literature. Thus Butler¹⁷⁸ reported 2 children with pyelonephritis in whom the concomitant hypertension was cured by nephrectomy. He emphasized the difficulty of differentiating between primary vascular and secondary renal hypertension. The two children had hypertension before any renal damage became evident, just as did the dogs Goldblatt described. Clinical findings very similar to those of experimental hypertension were reported by Barney and Suby,¹⁷⁹ of the Massachusetts General Hospital, Boston, in a patient with unilateral renal disease and arterial hypertension, who was apparently cured following nephrectomy. Since this patient suffering from unilateral renal disease associated with, and probably causing, arterial hypertension was cured for twenty-one months by nephrectomy, Barney and Suby suggested the importance of carefully studying and following up patients with unilateral renal disease, especially from the point of view of hypertension, both before and after operation. The results of their studies are as follows:

Since 1911, at the Massachusetts General Hospital there have been 305 patients with unilateral renal disease, on 224 of whom unilateral nephrectomy was performed. Seventy-six (25 per cent) had hypertension, with a preoperative systolic blood pressure of at least 140 mm of mercury.

Only 15 of these 244 patients could be followed with subsequent readings of blood pressure. Of these patients, all of whom were followed for four months to nine years after operation, 10 (67 per cent) showed an average drop in systolic pressure of 40 mm, as compared with the preoperative level.

177 Moore, F. H., and Allen, F. V. Vascular Clinics. Carotid Sinus and Hypertension, *Proc. Staff Meet., Mayo Clin.* **13** 747 (Nov. 23) 1938.

178 Butler, A. M. Chronic Pyelonephritis and Arterial Hypertension, *J. Clin. Investigation* **16** 889 (Nov.) 1937.

179 Barney, J. D., and Suby, H. I. Unilateral Renal Disease with Arterial Hypertension, *New England J. Med.* **220** 744 (May 4) 1939.

Chabanier and his associates¹⁸⁰ reported on surgical procedures in 49 patients with "nephroangiosclerosis." They discussed benign angiosclerosis, which is pure arteriosclerosis and is only seldom seen below the age of 60. They also discussed malignant nephrosclerosis, in which endarteritis proliferans is a feature. This is a disease of the young. Histologically, increase in elastic tissue and hypertrophy of the muscular wall are evident. In 29 of the 43 patients with malignant nephrosclerosis no arteriosclerotic element was detectable. This condition may start as symptomatic hypertension, but later, when tubules, glomeruli and interstitial tissues become involved, a nephritic picture develops, with appearance of albumin, casts and red cells. After this the average duration of life is five years. Hypertension with nephritis, then, may be due to malignant nephrosclerosis with glomerular manifestations or to chronic diffuse glomerulonephritis with secondary vascular changes.

The value of such findings lies in the fact that the diagnoses were based on the results of renal biopsies made during the operative procedures. The following surgical measures were used. 1. For the patient in a terminal stage, with marked renal insufficiency or cardiac decompensation, one kidney was decapsulated, if the patient improved, the other kidney was decapsulated, with section of the splanchnic nerve or renal denervation. 2. For the patient not in a terminal stage, section of the splanchnic nerve, adrenal denervation, decapsulation or removal of the aorticorenal ganglion has been done. The authors now favor combination of the last two methods.

The results of these procedures are given in too vague terms. The pressure arises again in most instances, but the symptoms of headache, palpitation and dizziness are relieved. This work would be quite inconclusive but for the excellent correlation of clinical pictures with the results of renal biopsies. In our clinic the results of such biopsies have now been studied for several years. It seems easier, however, to remove a small section of the kidney than to get a conclusive histologic report on it, as surgical specimens of this sort are rare. It will be necessary for such kidneys to be studied with special staining methods by men devoting themselves to this field.

Another attempt to revascularize the kidney in hypertension was reported by Abrami, Iselin and Wallick,¹⁸¹ who made unilateral omental transplants in 1 patient with chronic glomerulonephritis and 1 patient

180 Chabanier, H., Gaume, P., and Lobo-Onell, C. Vue d'ensemble sur les resultats d'interventions pratiquées dans 49 cas de néphroangioscléroses, *Presse med* **46** 1818 (Dec 10) 1938.

181 Abrami, P., Iselin, M., and Wallick, R. Essai de traitement de l'hypertension arterielle d'origine renale par la revascularisation chirurgicale du rein, *Presse med* **47** 137 (Jan 28) 1939.

with malignant nephrosclerosis. No clinical effect was noted in either patient after a few months. The authors expressed the belief that they were the first ones to have performed these operations, but at our clinic 3 such patients have been followed for several years. Essentially negative results are to be published shortly.

The effects of nonspecific operations on essential hypertension were studied by Volini and Flaxman¹⁸². They presented data on 27 patients who had had major operations such as cholecystectomy, hysterectomy and prostatectomy. They stated that all patients were relieved of headaches, pain in the chest, dizziness and fatigue, regardless of the operation performed. The duration of the symptom-free stage varied from four months to nine years, averaging three and a half years. The authors expressed the opinion that the results were better than those of any of the specific operations reported in cases of essential hypertension. They expressed a doubt whether surgical methods for the treatment of essential hypertension are ever justified.

An analysis of the tabulated results, however, does not reveal (1) the frequency of follow-up or (2) the extent to which cardiac decompensation and coronary insufficiency were the real factors in the fall of blood pressure. It is not clear how many symptoms these patients had referable to hypertension.

That rest in bed, anesthesia, loss of blood and psychic effect are all conducive to a lowering of blood pressure is obvious, but that bilateral herniotomy, for instance, done in a patient with a preoperative blood pressure of 250 systolic and 160 diastolic would result in freedom from symptoms for eight months is rather remarkable, some of the operations, such as prostatectomy with urinary obstruction and oophorectomy, may, of course, have a direct effect on hypertension.

AMPUTATION FOR VASCULAR DISEASE

Veal¹⁸³ reported on 110 patients who had amputations for arteriosclerotic gangrene, excluding patients with diabetes. With better preoperative care, earlier amputation and earlier mobilization, the mortality rate of 39 per cent dropped to 28.8 per cent. Pneumonia, shock and cardiac failure were the most frequent causes of death. Considering the type of material (Charity Hospital, New Orleans) the newer mortality rate is excellent.

182 Volini, J. F., and Flaxman, N. The Effect of Nonspecific Operations on Essential Hypertension, *J. A. M. A.* **112** 2126 (May 27) 1939.

183 Veal, J. R. Factors in the Mortality Rate of Arteriosclerotic Gangrene. Comparative Study of 214 Cases of Surgical Intervention, *J. A. M. A.* **110** 785 (March 12) 1938.

Taylor,¹⁸⁴ of the University of Indiana, also reported on efforts to reduce the high mortality from amputations. When the primary consideration is the saving of the patient's life, a simple guillotine amputation is indicated. Diabetes increases the mortality, in 77 amputations on 65 patients with this condition there were 30 deaths, a mortality of 38 per cent in regard to operations and 46 per cent in regard to patients. Among patients who had cellulitis, the mortality was 60 per cent. In the absence of diabetes 37 amputations resulted in 10 deaths, giving 27 per cent mortality for amputations and 35 per cent for patients.

The important point stressed by the author is the futility and danger of attempting to suture fascial layers over the bone. A loose closure of skin gave 27.7 per cent mortality, a primary fascial suture, 43.7 per cent. The first amputation can be readily made through the knee joint, with a secondary amputation above it when the infection has subsided.

It has been realized for some time that hospitals having an amputation service, in which all amputations are concentrated, show a decreasing percentage of mortality. Amputations properly performed are delicate surgical procedures. The determination of indications and of the proper level and the decision in regard to a one or a two stage amputation require an amount of experience which the casual operator hardly possesses. The quick rehabilitation of a crippled patient by means of temporary and permanent artificial limbs is an added duty of the surgeon.

During the last two years Allen has contributed an interesting series of experiments dealing with the beneficial effect of refrigeration of limbs deprived of their circulation. In the latest report¹⁸⁵ he suggested refrigeration of limbs that are to be amputated for the relief of pain, to enable the surgeon to apply a tourniquet and thus eliminate absorption. The author based his suggestions on animal experiments and stated that the exact clinical benefits or limitations await trial. It is an interesting thought which should be approached with considerable caution.

184 Taylor, F. W. Amputation Stump of Arteriosclerotic Gangrene, Surg., Gynec. & Obst. **67** 114 (July) 1938.

185 Allen, F. M. Experiments Concerning Ligation and Refrigeration in Relation to Local Intoxication and Infection, Surg., Gynec. & Obst. **68**.1047 (June) 1939.

News and Comment

Internships Open in California—The California State Personnel Board is seeking persons well qualified for employment as student intern and senior intern. There is no residence requirement for examination, and no written test will be given. Applicants will be rated on education, experience and scholastic record. Applications may be filed with the executive officer, State of California Personnel Board, 1025 P Street, Sacramento, at any time during the current year and will be rated immediately. If a candidate's qualifications are acceptable, his name will be placed on the list of those eligible for employment in accordance with his rating.

Bulletin of the Société d'Endocrinologie—The *Annales d'endocrinologie*, the official bulletin of the Société d'Endocrinologie was established this year, the first number being published in March. The editorial committee consists of Guy LaRoche (editor in chief), R. Courrier, J. DeLarue, Justin Besançon, E. May, L. Portes, C. Richet, P. Santon, H. Simonnet and H. Stevenin.

Book Reviews

William B Wherry, Bacteriologist By Martin Fischer Price, \$4 Pp 293
Springfield, Ill Charles C Thomas, Publisher, 1938

When Martin Fischer elected to write the biography of his friend, associate and contemporary William B Wherry, he added another quiet chapter to modern medical history. It is a pity that the layman, so obviously hungry for information about the progress of medicine and the biologic sciences, should not be fed his facts through the pleasing medium of biography rather than the less reliable medium of autobiographic confidences. No man, no matter how excellent his intentions, can properly weigh the human values in his memories of himself, it is to the distinct advantage of society when some Boswell is available who is willing and eager to write the story as he knows it.

Wherry was born in India in 1874, the son of American missionaries. His parents were well educated and poor. When William was 14 years old the parents moved back to the homeland to provide an education for their children. Rev Elwood Wherry resigned from his missionary work in foreign fields and obtained the promise of a position for himself with the American Tract Society. He settled in River Forest, Ill, just west of Chicago, and built a home on Ashland Avenue, which was for many years to function as the only permanent postoffice address of an always widely scattered family. Young William tramped the still unsettled west side districts of Chicago with a notebook and pencil, the "seeing eye" of the innate scientist was already his.

At 19 he entered Washington and Jefferson College, his father's Alma Mater, and in four years, on an unbelievably slim purse, he received his degree of Bachelor of Arts. In the autumn of 1897 he entered Rush Medical College, where for the first time he was to meet his future biographer. The days of his attendance were the heydays of Rush, the days of its great teachers, dedicated "to the common purpose of producing capable doctors—men able to meet a medical situation, whatever its nature, wherever found." Fischer writes of his and Wherry's school days there with comforting nostalgia, it is too easy to sneer back at the past from the heights of one's own achievements.

During his second year Wherry knocked and gained admittance at the laboratory of pathology, presided over by Prof Ludvig Hektoen. Hektoen had been taught the ultimate in morphologic pathology, but he taught his pupils something contrary. Morphology was dead, he said. Progress lay in bacteriology, in immunology, in experimental medicine and in dynamic concepts of disease. Here in Hektoen's laboratory Wherry met E R Le Count and G H Weaver, H Gideon Wells and E C Rosenow, D J Davis, Peter Bassoe, Brown Pusey, H T Ricketts, R T Woodyatt, Alice Hamilton and Martin Fischer. It is difficult to picture a happier association than that which must have been experienced between this dynamic leader and his alert disciples.

Wherry got his degree of Doctor of Medicine from Rush in 1901 and went from medical school to Dr E O Jordan's laboratory on the University of Chicago campus. There he earned his first salary, \$1,000 a year, established a firm friendship with Dr Jordan and met as a pupil Marie Eleanor Nast, of Cincinnati, whom he was later to marry. Through Dr Jordan he became interested in tropical disease, and because of Miss Nast, in the hope of eventually being able to support a wife, he applied for and won a research position in the government laboratories in the Philippine Islands. In Manila he worked with Paul G Woolley, of Johns Hopkins University, with whom he was later to be associated in Cincinnati. This

period was rich in experience and filled with valuable results, but it brought with it no financial security, and Wherry returned to the mainland after three years in the Philippines with his pockets still empty

The story of the next few years is the chronicle of almost all well trained young scientists who ask only a living and a laboratory from life. The tragedy lies in the fact that the living they demand is so pitifully small and so difficult to acquire. Wherry, perhaps, was more fortunate than many. At any rate, he progressed. He got an assignment in Anaconda, Mont., to investigate the cause of the mysterious deaths of countless cattle whose owners were suing the Copper Mining Company for responsibility. When his investigations in Montana were completed he was invited to Oakland, Calif., as professor of bacteriology in the medical school there. Martin Fischer was in Oakland and instrumental in Wherry's appointment. In December 1906 Wherry married Marie Eleanor Nast, who now had the degree of Doctor of Medicine from Johns Hopkins University, and the two went from Cincinnati to Oakland, where both medical Wherrys had teaching appointments in the medical school. William B. Wherry, the professor of bacteriology, had been there for only four months when he was summoned to San Francisco. There was bubonic plague on the Pacific Coast, and the bay cities were in quarantine. Wherry was asked to come to San Francisco to discover its source. He organized a fight against San Francisco's rats, inspected and performed autopsies on the human dead, surveyed about a million and a half properties, reduced morbidity and mortality, brought a lift of the quarantine—and was dismissed. The city had gone far enough, but Wherry was not satisfied with the results. Plague broke out in Seattle and was discovered inland in California, away from the water fronts. Finally, it was found in the ground squirrels which infested the western states. Wherry's conclusion that bubonic plague was endemic on the West Coast, which should be protected against itself rather than from the rats on incoming ships, was serious. It was more difficult to wage war against the thousands of independent squirrel hunters who persisted in the pleasures of individualism than against the helpless rats in San Francisco's sewers.

In 1909, on nomination of Paul G. Woolley, who was already installed at the University of Cincinnati, Wherry was invited to become the bacteriologist in the department of pathology at the reorganized medical school there. The salary offered was \$1,800 a year. The business of being only an assistant professor did not disturb him, but he wanted time away from his teaching for independent research and stipulated for financial support equal to what he was receiving at Oakland, Calif. Cincinnati offered \$2,400, and Wherry accepted. During the next year Martin Fischer joined the staff. Wherry was happy. He wrote of the situation to his mother, who replied, "It must be very nice indeed for so many of you young fellow-student doctors to be working in the same place."

Wherry had arrived. He was 35 years old, he had a wife and a growing family and a salary of \$2,400 a year. And he had a teaching position which he enjoyed and a laboratory which he could use. His work on tularemia and his studies on oxygen tension were done there. As his name became more widely known and his work more publicized, he had opportunities to go elsewhere. But his interests and loyalties were with the school in whose reorganization he had played an important part.

He died in Cincinnati in 1936 at a little less than 62 years of age. He had led a pleasant as well as a valuable life. His early attempts with the naturalist's notebook in the woods west of Chicago had developed into a taste for sketching and later to successful experiments with brush and canvas. He had played with as great a zest as he had worked. He maintained throughout his life his friendships and old loyalties and found time for new ones. The *Cincinnati Post* editorialized his life on the day of his death. "He died here Sunday, unknown to the general public. But that is as he wanted it. His scientific work was for use, not for the spotlight."

Practice of Medicine By Jonathan C Meakins, M D, LL D Price, \$12 50
Pp 1413, with 521 illustrations St Louis C V Mosby Company, 1938

The appearance of a new edition of a textbook about two years after the original edition was presented to the medical public indicates that the book was favorably received by the profession. It can be well understood why this is the case. Meakins has written a book on the practice of medicine which in the first edition had many things to commend it and a few features that might be criticized. In the second edition some changes, which on more mature consideration the author thought advisable, have been made, but they are few and far between. The original edition was so comprehensive and so well done that few alterations were necessary.

A feature thought most commendable in the first edition has been continued of course in the second, namely, a discussion of the symptoms and symptomatology of disease in the various systems of the body.

The explanation of the mechanism of production of these signs and the pathologic physiology concerned therewith is well worth the price of the book. For example, the physiologic disturbance resulting in dyspnea is excellently detailed and lucidly explained. On the other hand, I do not think it is necessary to incorporate a large number of reproductions of roentgenograms, which take up much space and make the book heavy and unwieldy. Most of the roentgen plates are good, but with few exceptions they add little to the value of the book. This feature has evidently been criticized, for in the preface to the second edition Meakins says that the depiction of rare conditions is an important feature of the book. Such illustrations may appear properly in a system or encyclopedia of medicine, but it hardly seems necessary to burden a tome which is obviously intended for a textbook with colored reproductions of unusual lesions, which frequently are nothing more than pathologic curiosities and which in many instances could be diagnosed at a glance.

In the preface, certain additions made in the second edition are specifically mentioned, namely, discussions of acute laryngotracheobronchitis, tuberculous tracheitis, "cysts" of the lung, Friedlander's bacillus pneumonia, lipoid pneumonia, monocytic leukemia, nutritional edema, protamine zinc insulin, experimental nephritis, vascular renal failure, congenital aplasia of the kidney, uremic state, sulfanilamide therapy, lymphogranulomatosis inguinalis, epidemic pleurodynia and Cannabis indica intoxication. With these additions the book seems to be a complete textbook. A study of the index and reference here and there to the text shows that little seems to be omitted or neglected which might be of interest and value to the practitioner or student.

Sulfanilamide Therapy of Bacterial Infections By Ralph R Mellon, M D , Paul Gross, M D, and Frank B Cooper, of the Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh Price, \$4 Pp 398, with tables and graphs Springfield, Ill Charles C Thomas, Publisher, 1938

Advances in the knowledge of the types, actions, uses and chemotherapeutic implications of the sulfanilamide compounds have been so rapid that the need for a comprehensive summary of the facts has become very real. This need has been well met by the authors of this book in their first section, which comprises a review, with a bibliography, of all the literature on the sulfonamide group of drugs. This review should be immensely useful to both clinicians and laboratory workers in various phases of chemotherapeutic research. The clinician will be particularly interested in the chapters devoted to the indications, routes of administration, schemes of dosage, toxic manifestations and results of sulfanilamide therapy in various infections.

The second section of the book deals with the authors' experiments on the bacteriostatic action of sulfanilamide and emphasizes the great discrepancies between the in vitro and the in vivo effects of the drug. Some possible factors

producing this difference—variations in the dose of the infecting organism, the virulence of the particular strain of the organism and the fitness or resistance of the host—are discussed

The third section details the authors' experiments designed to explain these differences. They show that, while physiologic solution of sodium chloride and blood serum containing dilutions of sulfanilamide in concentrations as high as 1:4,000 have only slight bacteriostatic effects on small and moderate-sized inoculums of several strains of streptococci and colon bacilli, the addition of small amounts of physiologic solution of sodium chloride to human serum produces virtual sterilization of such inoculums. This effect far exceeds a simple summation of the bacteriostatic effects of salt solution and human serum taken singly. The phenomenon is termed by the authors potentiation and explains the differences, at least in part, between the *in vivo* and the *in vitro* actions of sulfanilamide. It offers a particularly tempting explanation of the great efficacy of sulfanilamide in low dilution in the urine against infections of the urinary tract due to *Escherichia coli*.

The remaining section of the book is devoted to a consideration of biologic controls in chemotherapeutic work. Addenda are given which review the articles published while the work was in press.

The book is nicely planned and is printed in large, easily read type. It can be recommended to workers in all branches of medicine.

Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance
A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System By Charles Fisher, Ph.D., W. R. Ingram, Ph.D., and S. W. Ranson, Ph.D., M.D. Price, \$5. Pp. 212, with 71 illustrations. Ann Arbor, Mich. Edwards Brothers, Inc., 1938.

This monograph is concerned with the nervous and hormonal factors involved in the regulation of water balance and especially with the great increase in water exchange which characterizes the disease known as diabetes insipidus. The investigations were carried out in the Institute of Neurology of Northwestern University Medical School during the past six years. Although most of the facts presented have been published by the authors in various periodicals, it is highly pleasing to find them correlated and collected into one volume.

The principal method of study was the production of discrete lesions in various parts of the hypothalamus with the Horsley-Clarke stereotaxic instrument. Diabetes insipidus was produced in 85 cats and 2 monkeys. Among the final conclusions of the investigators are that the neural lobe of the hypophysis is an endocrine gland which plays an antidiuretic role in renal water balance and that diabetes insipidus is essentially a hypophysial deficiency syndrome caused by a diminution or by absence of the antidiuretic hormone of the neural lobe when the latter is extirpated or becomes atrophic secondary to interruption of the supraoptico-hypophysial tracts.

Essentials of Pathology By Lawrence W. Smith and Edwin S. Gault. Price, \$9. Pp. 886, with 679 illustrations (160 plates). New York: D. Appleton-Century Company, Inc., 1938.

This handsome volume represents an attempt to teach pathology by emphasis on the case history method. After short introductory paragraphs on the various conditions, a case history with a pathologic report is added. Some case reports are accompanied by illustrations. While this method is worthy of commendation, specific case studies are usually furnished in the practical part of any course in pathology and the textbook perhaps should deal with the subject in a more reflective, general and philosophic manner. However, the book is of interest, and the illustrations are especially good.

REFLEX CORONARY ARTERY SPASM FOLLOWING SUDDEN OCCLUSION OF OTHER CORONARY BRANCHES

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The serious effects of coronary artery disease on the heart are due to an inadequate blood supply to the heart muscle. Usually the reduction in the blood supply is associated with a diminution in the caliber of the coronary arteries, either local or general, by atherosclerosis. On the other hand, there are conditions which, even in the presence of normal coronary arteries, may result in a decreased blood supply to the myocardium¹

It is possible, also, that myocardial ischemia may result from temporary spasm of coronary arteries. This could take place, as a result of a decrease in or loss of the dilator response of the coronary arteries to physiologic stimuli, whether the arteries were atherosclerotic or normal.

Although it has been impossible so far to reproduce experimentally true human coronary sclerosis, it is possible to simulate the effects of the resulting myocardial ischemia by ligation of one or more branches of a coronary artery in the dog. Many authors have reported on the pathologic changes resulting from acute ligation of coronary arteries in different species of experimental animals. This literature, covering over one hundred years, has already been reviewed²

With the advent of the string galvanometer (1903) accurate electrocardiograms were made possible, and in later years the electrocardiographic changes following experimental coronary artery occlusion were studied by many persons. The results of such experiments have been used widely in the interpretation of clinical findings, particularly after

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From the Department of Medical Research, Banting Institute, University of Toronto Faculty of Medicine

1 White, P D. Heart Disease, New York, The Macmillan Company, 1934

2 Hall, G E. Relation of the Parasympathetic Autacoid to Cardiac Disease, Thesis, University of Toronto, 1936

Herrick³ had shown that coronary thrombosis was a clinical entity which could be recognized during life

The earlier workers conducted their experiments on anesthetized animals and naturally were unable to demonstrate pain following coronary occlusion. Other workers, including Sutton and Lueth,⁴ have described experiments in which occlusion of the coronary arteries in conscious dogs caused pain, nausea and vomiting. It has also been found that temporary occlusion caused pain, apparently the result of a sudden decrease in the blood supply to the heart muscle. Complete occlusion in conscious dogs, however, does not lead to permanent pain.

It is important, at this point, to consider whether temporary ischemia of the myocardium will produce persistent changes in the heart muscle. The work on cats recently reported by Blumgart and his associates⁵ showed that when temporary occlusion was maintained for fifteen minutes or more electrocardiographic changes persisted for at least twenty-two days. When the occlusion was maintained for five to ten minutes the electrocardiographic changes lasted for five to ten days. The first electrocardiographic changes characteristic of ischemia occurred within one minute. In dogs they found no gross or microscopic evidence of necrosis following temporary occlusion lasting from five to twenty minutes. When the occlusion was maintained for longer periods definite areas of necrosis were evident.

Thus an explanation is possible for the occurrence of electrocardiographic and, later, histologic changes in the myocardium of patients in the absence of coronary thrombosis.

It is well known that many patients with or without a history of angina pectoris die suddenly of a "heart attack." In many cases no evidence of coronary thrombosis can be obtained at autopsy. There is also a fairly large group of cases in which the severity of the symptoms of "coronary disease" is out of all proportion to the extent of the pathologic changes found in the coronary arteries or to the size of the infarcted area as observed at autopsy.

The purpose of the present paper is to report experiments which indicate that the high mortality following acute occlusion of one branch of a coronary artery in the conscious dog cannot be accounted for by the extent of the experimentally produced infarct. This work suggests

3 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* **59** 2015 (Dec. 7) 1912. Thrombosis of the Coronary Arteries, *ibid.* **72** 387 (Feb. 8) 1919.

4 Sutton, D. C., and Lueth, H. *Disease of Coronary Arteries*, St. Louis, C. V. Mosby Company, 1932.

5 Blumgart, H. L., Hoff, H., Landowne, M., and Schlesinger, M. J. Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries, *Tr. A. Am. Physicians* **42** 210, 1937.

that such mortality is the result of the development of a relatively large area of ischemia, brought about by spasm of collateral arterial branches, in addition to the original ischemic area

EXPERIMENTS

Normal healthy dogs of varying ages were used. Electrocardiograms were taken on at least three successive days before operation and at desired intervals following coronary artery occlusion. In some of the animals readings of the blood pressure were obtained by direct femoral puncture before, during and after the experimental occlusion.

The animals which did not survive the occlusion were examined immediately after death, and the location of the ligature and ischemic areas was verified. The gross findings were recorded on a mimeographed diagram of the dog heart. Histologic sections were taken from various areas of the hearts of all the animals used.

Each surviving animal was kept lying quietly on his side for one to two hours after the ligation. After this period the animal was removed to its cage and no restraint was made on its movements. In view of the already weakened myocardium, any excessive exertion might readily have resulted in cardiac failure or rupture. In spite of this possibility the death of any animal which died within twenty-four hours of ligation was listed as sudden death.

Electrocardiograms and records of the blood pressure were taken for the surviving dogs for as long as nine months after the experimental occlusion.

For operation, $\frac{1}{4}$ grain (0.16 Gm.) of morphine and ether administered intratracheally were used in all cases. An aseptic technic was employed. After careful dissection a ligature was passed under either the proximal portion of the anterior descending branch or the circumflex branch of the left coronary artery. A special ligature carrier was used for this purpose, so that pulling, rolling or constriction of the artery would be prevented.

Four groups of animals were prepared in this way. In group 1 the anterior descending branch was completely ligated. In group 2 the circumflex branch was ligated. In group 3 a ligature was placed around the anterior descending branch and loosely tied with a single knot. The two ends of the ligature were brought to the surface of the chest at the ends of the incision, the chest was closed and the superficial layers were sutured. A sufficient length of slack ligature was left within the chest so that movement of the heart would not tighten the loose knot. After a sterile dressing was applied to the wound the animal was allowed to recover from the anesthesia. In group 4 a loose ligature was placed around the circumflex branch and the animal treated as in group 3.

On the day following the operation each animal in groups 3 and 4 was placed on its right side. Electrocardiograms were taken and the two ends of the loose ligature pulled tightly. The ends of the ligature protruding through the chest wall were cut, so that the heart would not be pulled permanently out of position. Thus acute occlusion of a branch of a coronary artery in the conscious dog was effected.

GROUP 1—Sudden occlusion of the anterior descending branch of the left coronary artery during anesthesia

Seventeen dogs, including 7 litter mates 6 months of age, were used in this series. The anterior descending branch was ligated $\frac{1}{2}$ inch (1.27 cm) from the aorta. Electrocardiograms were taken before, during and at intervals after the ligation.

Only one death occurred in this group. On the basis of this figure one might expect a mortality of less than 10 per cent.

Pathologic Changes—In order to follow the pathologic changes occurring in the heart, the animals were killed one-half, two and one-half and twelve hours and two, three, seven, fourteen and twenty-one days after the occlusion. Routine sections were taken for microscopic examination from the infarcted and normal areas of each heart.

Gross examination revealed that few changes had taken place in the heart muscle thirty minutes after ligation. Within two and one-half hours, however, the infarcted area became dark and hard and could be differentiated readily from the surrounding myocardium. At seven days the infarcted area appeared dark, soft and very weak (fig 3A). It is at this period that rupture of the ventricle would most likely occur. Considerable fibrosis was evident at fourteen days, and by twenty-four days the infarcted area was noticeable only as a dense, whitish contracted scar.

The progressive microscopic changes which take place in the myocardium after occlusion are illustrated in figures 1, 2 and 3.

Within thirty minutes after occlusion variations in the staining quality of the muscle were noticed. These alterations in staining occurred frequently within single muscle fibers. Evidence of capillary hemorrhage was usually present. Sections taken from noninfarcted areas in the same heart did not show these changes. This type of early degeneration (early hyalinization) of the myocardium has been observed in dogs when a chronic autonomic imbalance has been produced by prolonged administration of acetylcholine⁶ or by prolonged stimulation of the vagus nerve.⁷

The alterations in the staining qualities became more pronounced within a few hours. By two and one-half hours (fig 1A) swelling of the muscle fibers was apparent. The nuclei also began to show changes in size and staining. The arterioles in the infarcted area appeared narrow but well filled with blood cells.

At ten hours (fig 1B) more marked degeneration was evident. Many leukocytes were scattered throughout the section. The muscle fibers were pale staining and showed a definite loss of striations. The nuclei were undergoing marked

6 Hall, G. E., Ettinger, G. H., and Banting, F. G. An Experimental Production of Coronary Thrombosis and Myocardial Failure, *Canad. M. A. J.* **34**: 9, 1935.

7 Manning, G. W., Hall, G. E., and Banting, F. G. Vagus Stimulation and the Production of Myocardial Damage, *Canad. M. A. J.* **37**: 314, 1937.

degenerative changes. All these changes were more advanced at the end of twenty-four hours, while at forty-eight hours early fibroblasts were seen growing into the infarcted area (fig 2 *A*). The number of fibroblasts increased rapidly, as shown by the seventy-two hour section (fig 2 *B*).

Sections taken from the infarcted region of the seven day specimen showed areas of complete necrosis surrounded by fibroblastic proliferation (fig 3 *A*). Many small blood vessels were present. By the end of the second week the area of necrosis had become replaced by ingrowing fibroblastic tissue. The fibroblasts were now smaller and older, and the amount of intercellular matrix had increased.

Sections of an infarcted area taken twenty-two days after ligation showed fairly dense areas of scar tissue (fig 3 *B*). The tissue was less cellular in appearance, and the fibroblasts were of the adult type. Typical bands of collagen made up the greater portion of the area.

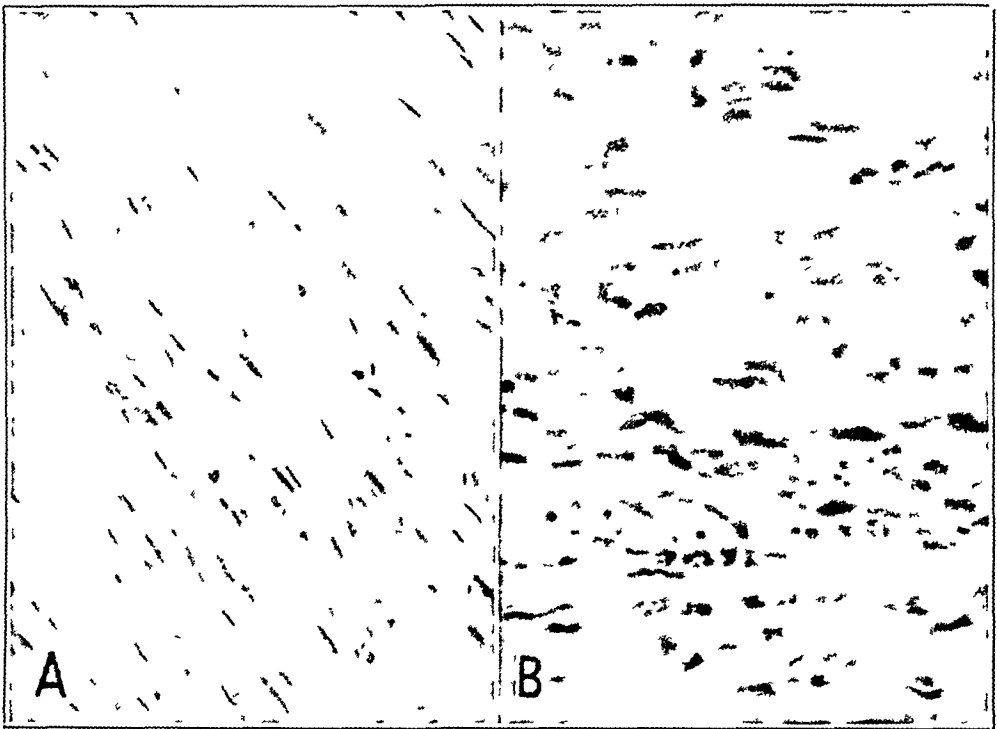


Fig 1—Portions of early infarcts. *A*, two and a half hours after ligation. *B*, ten hours after ligation.

Electrocardiographic Changes—The typical changes which occurred after the sudden ligation of the anterior descending branch were an elevation of the RT segment in lead I (high take-off) and a depression in leads II and III (low take-off), indicative of infarction on the anterior surface or apical region of the heart. The depression of the ST segment, with a low take-off, in lead II was especially characteristic of this group. Progressive alterations in the contour and the direction of the T waves were observed in all cases. Ventricular extrasystoles were infrequently seen after the ligation. In only 1 case was there any evidence of axis deviation. This was in contrast to the common finding of left axis deviation with occlusion of the circumflex branch.

The changes in the RT segment of the ventricular complex, although sometimes marked, were frequently transient, and in many instances the electrocardiograms showed that the heart had become relatively normal within a few days. Records were taken in some cases nine months after ligation.

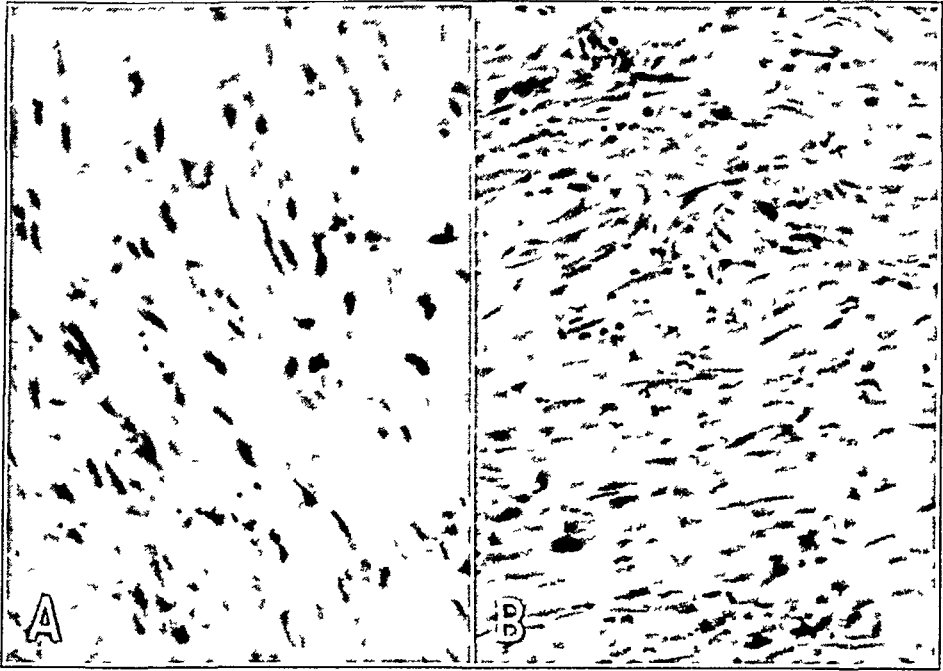


Fig 2—Portions of early infarcts *A* forty-eight hours after ligation *B*, seventy-two hours after ligation

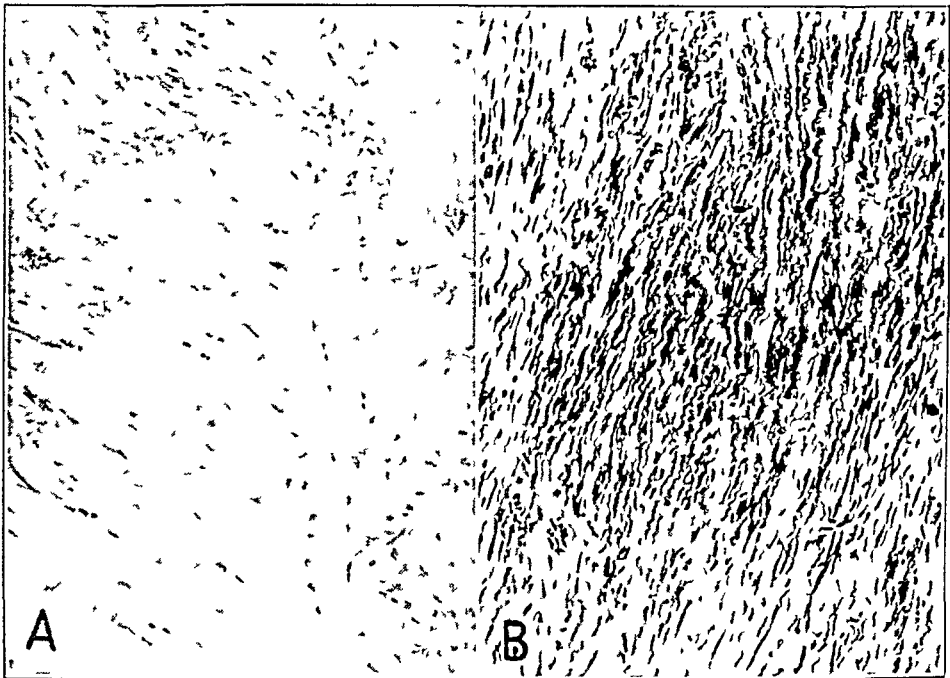


Fig 3—Portions of older infarcts *A*, seven days after ligation *B* twenty-two days after ligation

GROUP 2—*Ligation of the circumflex branch of the left coronary artery during anesthesia*

The circumflex branch was ligated in 23 dogs under morphine and ether anesthesia. Seventeen dogs survived and 6 died suddenly after the ligation.

Changes in Blood Pressure—In the animals which survived the occlusion the changes in blood pressure were fairly uniform. In one dog the pressure fell from a normal of 120 to 80 mm of mercury within two minutes of the occlusion and then gradually increased to 88 mm of mercury in the next three minutes. This level was maintained for about fifteen minutes. Then a more marked decrease occurred, and the blood pressure went as low as 55. Cardiac irregularities were noted at this time (fig 4). However, after a few minutes the pressure gradually increased, and twenty-two minutes after ligation it had returned to 100. The

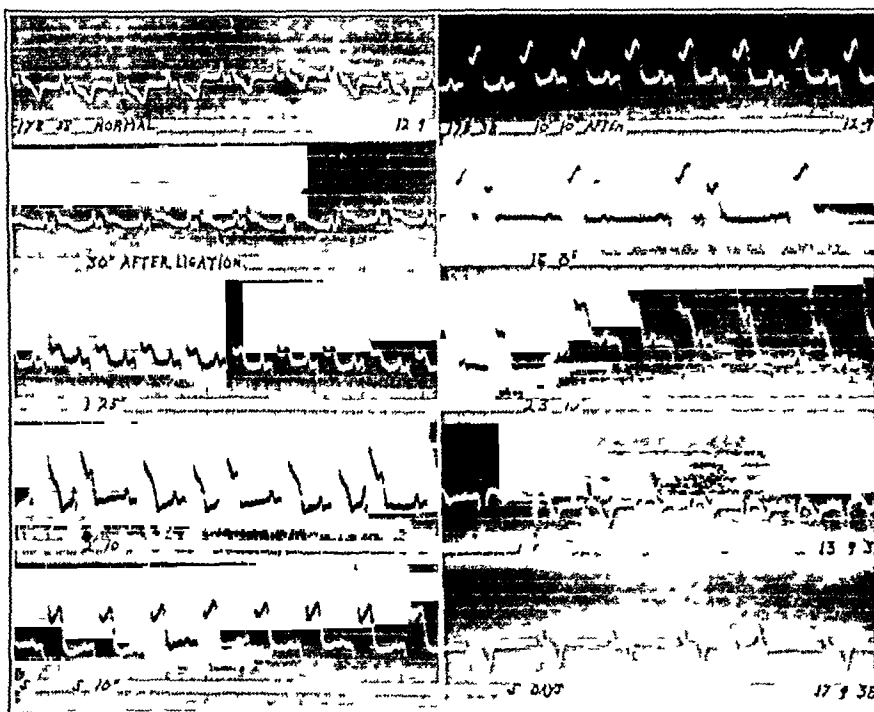


Fig 4—Lead II, showing progressive changes following acute ligation of the circumflex branch in the anesthetized dog. Note early elevation of the RT segment.

heart again became regular, and the pressure remained constant at 100 for at least thirty minutes longer.

The changes in blood pressure recorded for animals which did not survive the occlusion were likewise fairly uniform. In one dog the pressure fell to 80 within twenty-five seconds. This level was maintained for about six minutes, and then there was a sudden decrease to 40. This sudden drop coincided with the onset of ventricular fibrillation. Within a few seconds the blood pressure was zero.

Electrocardiographic Changes—The electrocardiographic changes which occurred after sudden ligation of the circumflex branch in the anesthetized dog were typical for the animals which recovered, and typical changes were recorded for those which did not recover.

Alterations in the direction and the contour, as well as the amplitude, of the T wave occurred within thirty seconds of occlusion (fig 4). There were progressive elevation of the ST take-off and disappearance of the isoelectric ST segment (leads II and III). This premonitory period may be very short or

extend over many minutes. The regularity of the heart was quickly disturbed by premature contractions of ventricular origin. This phase was coincident with the second fall in blood pressure. Infrequently partial block was evident, but this condition usually gave way to a series of extrasystoles.

In those animals which recovered the changes in the T wave persisted for about seven days and then showed a gradual altered inversion as the healing of the infarcted area progressed (figs 1 to 3). Marked left axis deviation (fig 5) was evident within twenty-four hours, and extrasystoles originating in the left ventricle were not infrequently found. The records indicated infarction of the posterior surface.

In the animals which died suddenly after the occlusion, the electrocardiogram showed an early alteration in the T wave and an elevation of the ST isoelectric segment in leads II and III. Single extrasystoles became apparent within a few seconds and were followed by definite groups of extrasystoles. Ventricular tachy-

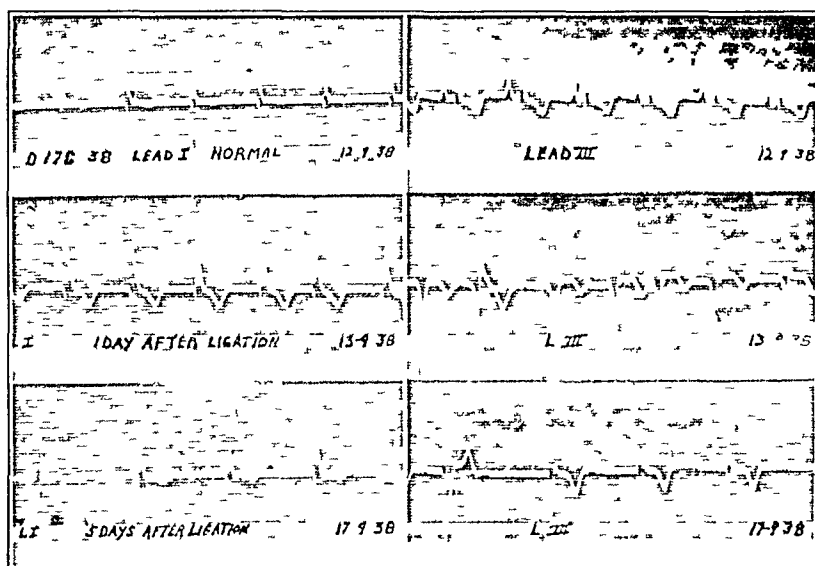


Fig 5—Leads I and III for the animal represented in figure 4, taken one and five days after ligation, showing left axis deviation

cardia, simple or complex, invariably followed the phase of extrasystoles. In some records the tachycardia passed gradually into fibrillation, while in others the transition was more abrupt.

As indicated previously, the blood pressure fell to zero with the onset of fibrillation.

Pathologic Changes—Immediate autopsy was performed on all dogs which died after the occlusion. The faint outline of the infarcted area could be distinguished, sometimes with difficulty, by the paleness of the area. No significant histologic changes could be detected.

The animals which recovered showed, when killed at a later date, changes in the heart muscle similar to those already described for corresponding time intervals in group 1.

Results—In this group of 23 animals, in which the circumflex branch was ligated with the animal under morphine and ether anesthesia, 17 survived and 6 died suddenly after ligation. This indicates a probable mortality of about 25 per cent.

GROUP 3—*Ligation of anterior descending branch of the left coronary artery in the conscious state*

In the 22 animals in this group, at least twenty-four hours after operation and anesthesia the ends of the ligature protruding through the chest were pulled tightly. This produced a sudden occlusion of the anterior descending branch of the left coronary artery. Electrocardiograms were taken before, during and at varying intervals after the strings were tightened.

Clinical and Electrocardiographic Changes—Typical signs of coronary occlusion, such as pain (indicated by whining and restlessness), dilated pupils and dyspnea, were observed. These signs were evident about sixty to ninety seconds after occlusion, and their appearance corresponded roughly with the onset of ventricular tachycardia. In 7 of the 22 dogs fatal ventricular fibrillation followed

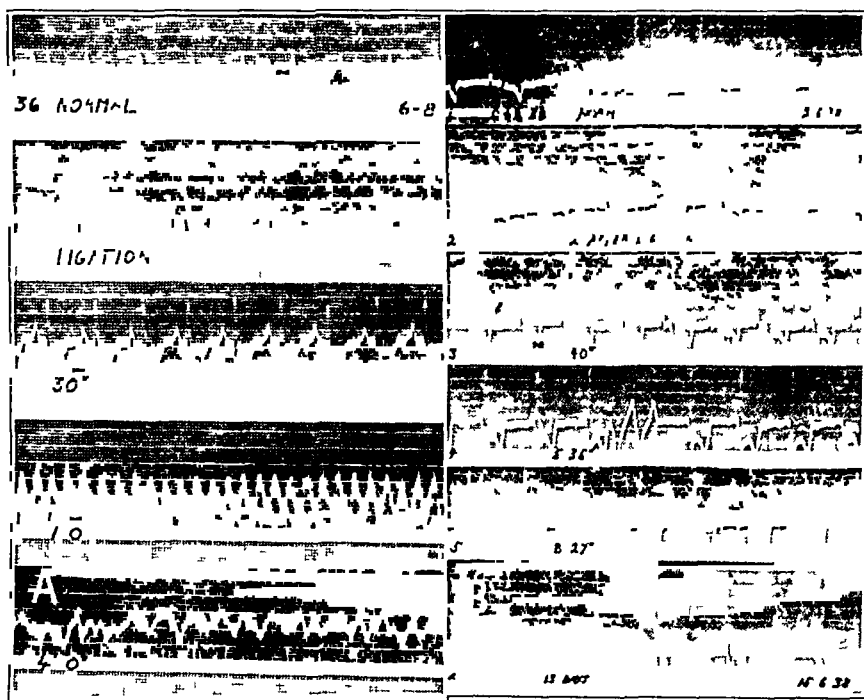


Fig 6—Lead II, showing changes following ligation of the circumflex branch of the left coronary artery in the conscious dog. Note early depression of the RT segment. *A*, fatal ventricular fibrillation. *B*, survival type of record.

the tachycardia (fig 6 *A*). Two other dogs died unobserved within twelve hours. Typical signs of infarction of the anterior surface were present in the records for all 13 dogs which recovered. Earlier changes occurred in the form, the amplitude and the direction of the T wave and in the depression (leads II and III) and elevation (lead I) of the ST isoelectric segment (fig 6 *B*).

Pathologic Changes—Since the mortality in this group was 40 per cent, as compared with less than 10 per cent in group 1, in which ligation of the same branch was performed with the animals under anesthesia, it seemed reasonable to suppose that some mechanism was involved which was capable of being eliminated by the anesthesia.

Immediate autopsy was performed on 6 dogs which died suddenly after the ligation. Besides the area of ischemia produced by the arterial ligation, one or more smaller pale grayish areas were seen in other regions. These areas resembled

the primary infarcted area except in location and size. No such ischemic-looking areas were observed in the hearts of dogs dying as the result of acute ligation of a coronary artery performed while they were under anesthesia.

GROUP 4—Ligation of the circumflex branch of the left coronary artery in the conscious state

Sudden ligation of the circumflex branch was effected in 16 dogs twenty-four hours after the preparatory operation. Electrocardiographic records were obtained before, during and after ligation. In 5 animals continuous readings of the blood pressure were obtained. All 16 animals experienced pain, as evidenced by whining, restlessness, excitement and dilatation of the pupils. Twelve animals died suddenly after the ligation. This mortality of about 75 per cent is to be compared to that in group 2 (ligation with anesthesia), in which the mortality was about 25 per cent.

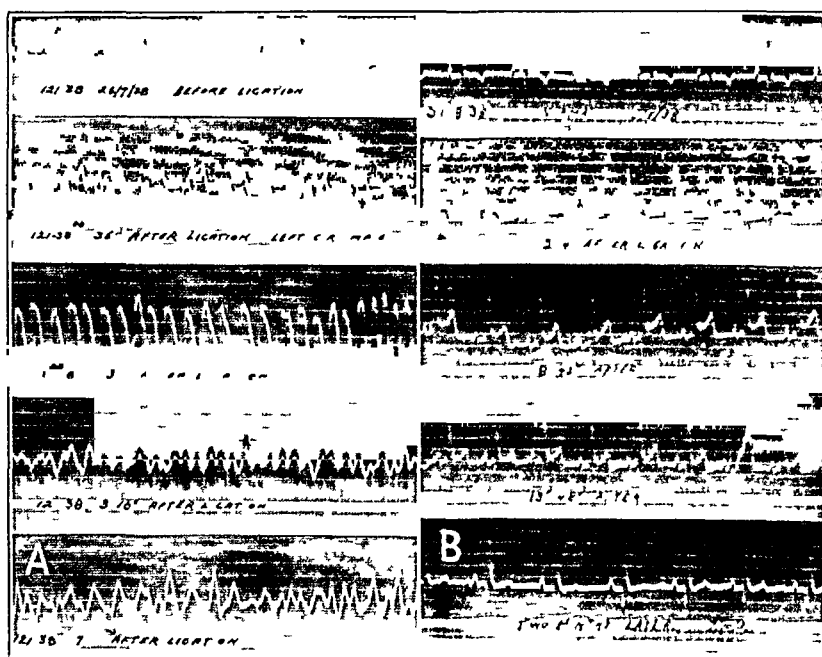


Fig 7—Lead II, showing changes following ligation of the circumflex branch in the anesthetized dog. In *A*, note early elevation of the RT segment, ventricular tachycardia and fatal fibrillation. *B*, survival type of record.

Changes in the Blood Pressure—In a typical case the blood pressure fell from a normal of 120 to 100 within five seconds of the ligation. (This first decline in pressure was observed in all cases of sudden occlusion of the coronary artery.) The blood pressure continued to fall, reaching a level of 70 within seventy seconds. At this point a sudden decrease to about 40 occurred, coincident with the onset of ventricular fibrillation. The decline in blood pressure to zero was then rapid.

It will be recalled that in the animals surviving ligation of the circumflex branch produced while they were under anesthesia (group 2) a second fall in blood pressure was observed. In these dogs the second decrease coincided with the onset of cardiac irregularities which did not continue to fibrillation. With the return of the heart beat to normal rhythm the blood pressure returned almost to normal.

In the few surviving animals in group 4, the second fall in blood pressure also coincided with the onset of tachycardia, but as fibrillation did not intervene

the pressure gradually returned to normal with the reestablishment of a normal cardiac rhythm

Electrocardiographic Changes—The typical electrocardiographic changes which occurred in 75 per cent of the animals in this group are illustrated in a series of lead II records taken before and immediately after ligation (fig 7A). Within thirty-five seconds a marked elevation of the ST isoelectric segment (leads II and III), with a change in the amplitude and contour of the T wave, was evident. Extrasystoles were followed by the onset of ventricular tachycardia, which was well established in ninety seconds. Fatal ventricular fibrillation rapidly intervened and continued, with gradually decreasing amplitude, for as long as fifteen to thirty minutes after its onset.

The electrocardiographic changes which occurred in the surviving animals (25 per cent) also showed elevation of the ST isoelectric segment (leads II and III), changes in the T wave and extrasystoles (fig 7B). Ventricular tachycardia and fibrillation did not occur. The late interval records are similar to those of group 2.

Pathologic Changes—The infarct produced by ligation of the circumflex branch differed from the one produced by ligation of the anterior descending branch only in location and size. In addition, one or more small ischemic-looking areas, independent of the primary infarct, were observed at autopsy. These areas, absent in the anesthetized dogs, also suggest that the higher mortality for the conscious animals is the result of a mechanism which is minimized by the anesthetic.

ADDITIONAL EXPERIMENTS—In order to eliminate the possibility that displacement and traction of the heart played some role in the increase of mortality following ligation of a branch of a coronary artery in conscious dogs, a series of animals was prepared as in group 4. After the chest was closed, but with the animal still under the anesthetic, sudden occlusion was produced by pulling the two ends of the loosely tied ligature. The mortality was the same as in group 2 (20 to 25 per cent), in which the ligation was completed in the open thorax with the animals under anesthesia.

COMMENT

In the dog the left coronary artery, after giving off deep septal branches, divides almost immediately into the anterior descending and the circumflex branch. The distribution of the anterior descending branch is comparable to that in the human being. The circumflex branch is, however, much the larger branch and supplies a greater area of the myocardium than either the anterior descending branch of the left or the right coronary artery. The circumflex branch supplies marginal and atrial branches and, continuing on to the posterior surface, becomes the posterior descending branch. In the human heart the posterior descending branch is the termination of the right coronary artery.

Thus, ligation of the circumflex branch of the left coronary artery produces infarction of a greater extent than ligation of any other branch, and electrocardiographic records after such ligation show evidence of posterior infarction. The right coronary artery, according to our experience, can be ligated without increasing the mortality beyond that expected in thoracic operations (less than 1 per cent). We have found also that

dogs in which the circumflex branch of the left coronary artery has been ligated while they were under anesthesia are relatively able to tolerate subsequent ligation of the right coronary artery. Similarly the right coronary artery can be fairly safely ligated in dogs which have had the anterior descending branch of the left coronary artery ligated while they were under anesthesia. None of the dogs survived when the third large branch was ligated at a later operation.

The collateral or anastomosing coronary circulation, as in the human heart, is much more abundant in the old than in the young. However, young dogs and pups, although this anastomosis is not nearly so well developed, are much more tolerant to occlusion of a large coronary artery than old dogs. This has been well illustrated in experiments during the past three years. For example, 2 old dogs in which the anterior descending branch of the left coronary artery was tied while they were under anesthesia died immediately after ligation, whereas many pups (3 months old) and young adult dogs readily survived this operation (90 per cent). It would seem, in general, that as the age of the animal increases the mortality following ligation of a coronary artery likewise increases. This possible complicating factor was eliminated in the present series by using young adult dogs in all groups, except in those cases specifically cited.

The experiments reported in this paper show, as others have previously shown, that large areas of the myocardium can be rendered ischemic by ligation of various branches of the coronary arteries in the anesthetized animal with a relatively low mortality. When similar ligations are performed in the conscious animal the mortality is greatly increased.

When the anterior descending branch of the left coronary artery is ligated in the anesthetized dog the mortality is less than 10 per cent. When the same branch is ligated in the conscious dog the mortality immediately increases to about 40 per cent. Similarly, when the circumflex branch is ligated in the anesthetized dog the mortality is about 25 per cent, while ligation of the same branch in the conscious dog is attended by a mortality of about 75 per cent, as shown in the accompanying table.

Mortality in the Four Groups of Experiments

Group	Branch Ligated	Anes- thesia	No of Dogs	Sudden Death				Delayed Death (Cardiac), 14 Days
				½ Hr	12 Hr	24 Hr	Mor- tality, %	
1	Anterior descending	Yes	17	1	0	0	<10	0
2	Circumflex	Yes	23	5	0	1	25	0
3	Anterior descending	No	22	7	2	0	40	1 (rupture)
4	Circumflex	No	16	6	3	2	75	1 (cardiac failure)

The primary infarct produced is of course relatively the same size in the anesthetized and in the conscious animal. Why then is there such an increase in mortality for the conscious dog? This may be brought about through several mechanisms. Perhaps the sudden accumulation of metabolites, with an increase in lactic acid at the expense of glycogen, in the ischemic area sets up afferent sympathetic impulses. These may, in turn, initiate efferent parasympathetic vasoconstrictor impulses which produce spasm of the medium-sized and the smaller coronary arteries and arterioles. This mechanism would result in the production of relatively large areas of ischemia secondary to the primary infarcted area. Under these conditions disturbed conduction and contraction are inevitable, and extrasystoles, tachycardia and fatal fibrillation, in that sequence, might conceivably follow.

If the secondary ischemia were less, the disturbances would likewise be lessened and fibrillation might not be initiated. Recovery would then be possible. The animals in groups 2 and 4 which did survive showed evidence of pain equal to that exhibited by the animals which did not survive. In the anesthetized condition, when pain could not be manifested, it is possible that such reflex spasm was prevented.

Additional support to the observation of reflex coronary artery spasm has been obtained in some preliminary experiments. A decrease in the rate at which blood flowed through the circumflex branch before, during and after sudden ligation of the anterior descending branch in the conscious animal was recorded in two instances. Whether this decrease was due to a reflex spasm of the distal arterioles or directly to the slight decrease in the mean diastolic pressure remains to be determined. Experiments will be presented in a future paper to show that the increase in mortality following ligation of a coronary artery in the conscious animal is not the result of changes in the systemic blood pressure.

From other preliminary experiments, in which smaller branches of the coronary arteries were ligated, it seemed that the apical region was the most sensitive to ischemia and that fibrillation was most readily produced when the blood supply to this region was decreased. Possibly this may be explained when more is known about the relation between the ventricular muscle bundles, the spread of electric activity through these muscle bundles and the factors which initiate the sequence of events which terminate in fatal ventricular fibrillation.

Although in these experiments fatal ventricular fibrillation occurred in all the animals which died suddenly after ligation of a coronary artery, it is possible that in a much larger series of experiments a few instances of sudden death from heart block would have been encountered. A few cases of sudden death from heart block, with actual electrocardiographic evidence, have been reported in the literature. The patients

were all known to have cardiac disease and perhaps had been receiving drugs, such as digitalis or quinidine

Experimentally we⁸ have shown that the administration of various drugs prior to acute ligation of a coronary artery in conscious animals diminishes the incidence of fatal ventricular fibrillation while increasing the incidence of fatal heart block

SUMMARY

The mortality following sudden occlusion of the anterior descending branch of the left coronary artery in the anesthetized dog is less than 10 per cent. For the conscious dog the mortality is about 40 per cent.

For sudden occlusion of the left circumflex branch, the mortality is about 25 per cent with anesthesia and about 75 per cent without.

The great increase in mortality for the conscious animal may be the result of a reflex spasm of collateral arterioles and small arteries producing additional areas of ischemia.

All the animals that died suddenly after ligation in the conscious state showed evidence of ventricular extrasystoles, tachycardia and fibrillation in that sequence.

⁸ McEachern, C. G., and Hall, G. E. Unpublished data.

ANGINA PECTORIS IN HEREDITARY XANTHOMATOSIS

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It has long been agreed that the various forms of xanthomatosis are of general medical interest and not simply the expression of a local change in the skin. In many cases deposits of the same structure as that of the cutaneous deposits occur in internal organs. In 1878 Quinquaud advanced the idea that xanthoma is due to changes in the blood, hypercholesteremia, and more recent investigations have established the fact that it does concern a disturbance of lipid metabolism.

Other forms of lipoidosis, such as Gaucher's disease and Niemann-Pick disease, will not be considered at this time, neither will the xanthomatous manifestations in diabetes, myxedema, pregnancy and disease of the liver with icterus be discussed.

The constitutional nature of "essential" xanthomatosis is shown clearly by its hereditary occurrence. Torok¹ observed xanthomatosis as a hereditary manifestation in several families, and this has since been confirmed by others. The localization of xanthoma in the internal organs, particularly in the biliary tract and the vascular system and notably in the coronary arteries and the cardiac valves, has been observed. Less frequent localization in various mucous membranes has been described also.

The earlier literature gives the impression that localization in the liver and biliary tract is more frequent and of greater clinical interest than localization in the vascular system. In 1873, however, Fagge² described a case of xanthomatosis with cardiovascular symptoms, and in 1889 Lehzen and Knauss³ reported the case of a girl 11 years old in whom steadily growing xanthomatous nodules, with signs of mitral insufficiency, had been observed since her third year. The girl died suddenly, and postmortem study revealed extensive xanthomatous deposits in the aorta, with narrowing of the isthmus as well as in other large arteries. Her sister, 9 years of age, also had cutaneous xanthomas.

1 Torok, L. *Ann de dermat et syph* **4** 1109, 1893

2 Fagge, C H. *Tr Path Soc London* **24** 242, 1873

3 Lehzen, G, and Knauss, K. *Virchows Arch f path Anat* **116** 85, 1889

Torok¹ mentioned several fatal instances of xanthomatosis with cardiovascular disease. A number of subsequent observations of similar import have been published by various authors.⁴ They concern mostly young persons or persons in their best years who died suddenly from heart disease, the anamnesis revealing other instances of the same nature in the families. In addition to xanthomas, hypercholesteremia has been demonstrated in many of these patients as well as in their relatives.

My attention was directed to this form of cardiovascular disease by the publications by Harbitz^{4b} of his results of extensive and thorough studies of cases in Norway. In all previous publications about hereditary xanthomatosis associated with heart disease, the authors have seemed to take for granted that the condition is decidedly infrequent. I observed my first patient with xanthoma tuberosum and angina pectoris in April 1937, and by June I was able to make a preliminary report of a number of cases in which I expressed the opinion that hypercholesteremia is a frequent and important factor in heart disease.⁵ This opinion has been strengthened beyond expectation by the study of additional patients, many of whom have been referred to me by my colleagues. The article by Montgomery⁶ also has confirmed my opinion. He has discussed 26 cases of xanthoma tuberosum, in nearly half of which there were cardiovascular symptoms. In these cases and in 45 cases of palpebral xanthelasma, Montgomery demonstrated cholesteremia. He has stated that cardiovascular and other systemic disturbances are frequent in palpebral xanthelasma. He has also observed a frequent familial disposition in his cases.

In my cases the xanthomatous deposits occurred as xanthelasmas on the eyelids and as xanthoma tuberosum. Palpebral xanthelasma is the more frequent (fig 1) and occurs oftener in women than in men. Not infrequently xanthoma tuberosum is present at the same time, and as these two deposits have the same structure, they may be regarded as external localizations of the same process. Xanthoma tuberosum appears as nodes of variable size and number on the extensor surfaces, most frequently on the fingers, the elbows, the tibial tuberosities and the achilles tendons and less frequently elsewhere (figs 2 and 3). The nodes may be quite minute (fig 4) and hence are easily missed. They are as a rule multiple and may be so large as to cause deformities and cosmetic

4 (a) Arning, E, and Lippmann, A. *Ztschr f klin Med* **89** 107, 1920

(b) Harbitz, F. *Norsk mag f lægevidensk* **86** 321, 1925, **97** 695, 1936, **98** 1317, 1937, Tumors of Tendon Sheaths, Joint Capsules and Multiple Xanthoma, *Arch Path* **4** 507 (Oct) 1927, Ueber plotzlichen Tod mit natuerlicher (d h nicht gewaltsamer) Todesursache, insbesondere bei jungen Leuten, monograph 5, Norske Videnskapsakadem i Oslo, Matematisk-Naturvidenskabelig Klasse, 1938

5 Muller, C. *Acta med Scandinav*, 1938, suppl 89, p 75

6 Montgomery, H. *Proc Staff Meet*, *Mayo Clin* **12** 641, 1937

as well as mechanical disturbances (figs 5 and 6) The consistency may vary greatly Below the knee the hardness may simulate a bony overgrowth of the tibial tuberosity The nodes do not infiltrate the skin, which retains its usual color, but if the skin is stretched, the yellow of the xanthoma may be seen The nodes are usually lobulated or finely granular and intimately connected by infiltration with tendons, fascia or periosteum The growth is slow and gradual

The diagnosis of palpebral xanthelasma as a rule is easily made, but the condition may be overlooked, especially when the skin is wrinkled Xanthoma tuberosum is differentiated without difficulty from Heberden's nodes and from deposits of uric acid but may be confused with the pads on the fingers described by Gailiod⁷ These nodes (fig 7) are composed of fibrous tissue and occur on the dorsal sides of the joints between the first and second joints of the fingers (never on the thumb) These pads are not uncommon and may occur in families



Fig 1 (case 13) —Xanthelasma of the eyelids

It is noteworthy that in xanthomatosis, arcus senilis is frequent, even when the patients are young

The xanthoma deposits contain cholesterol, 24.9 per cent of the dried mass, phosphatide phosphoric acid, 0.26 per cent, and fat, 20.4 per cent⁸

Xanthoma tissue is composed of large, so-called foam cells, which contain lipoids, inflammatory cells of various kinds, including giant cells, products of the reaction of the tissue to the lipid deposits, and in the latter stages connective tissue It seems to be the general opinion that the arteriosclerotic lesions in xanthomatosis cannot be distinguished either grossly or microscopically from the lesions of common arteriosclerosis

⁷ Garrod, A. E. St Barth Hosp Rep **29** 157, 1893, Brit M J **2**:8, 1904
White, H., and Hale Quart J Med **1** 479, 1907-1908

⁸ Raeder, G. Norsk mag f lægevidensk **97** 113, 1936

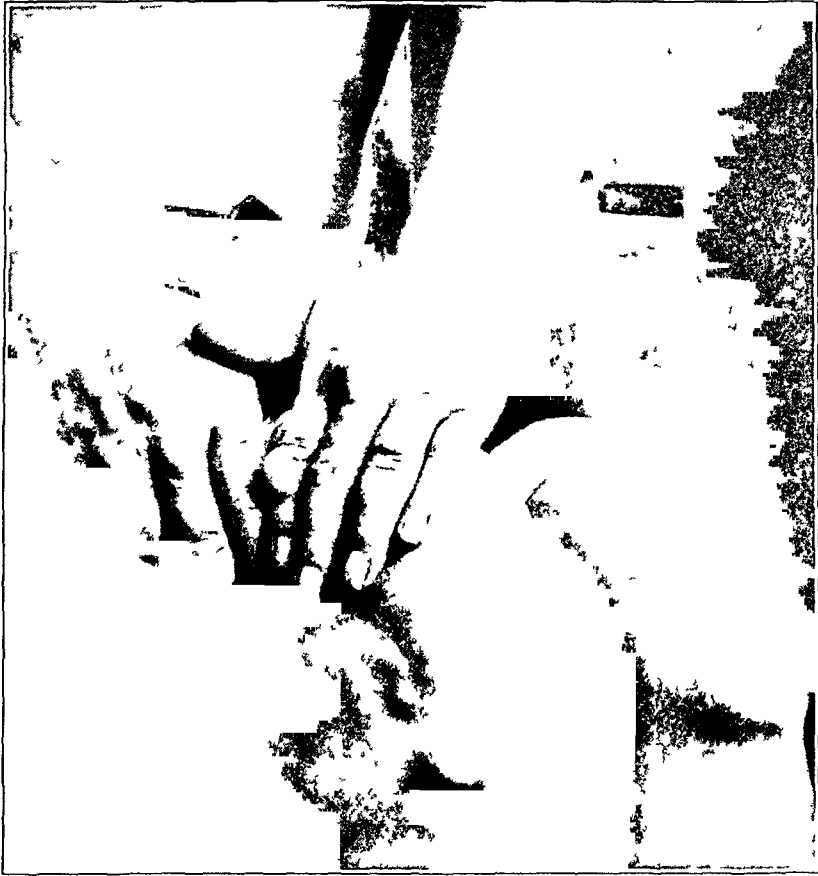


Fig 2 (case 17, family 5) —Xanthoma tuberosum Besides the nodes on the elbows, fingers and knees, there were deposits also on the achilles tendons and xanthelasma of the eyelids

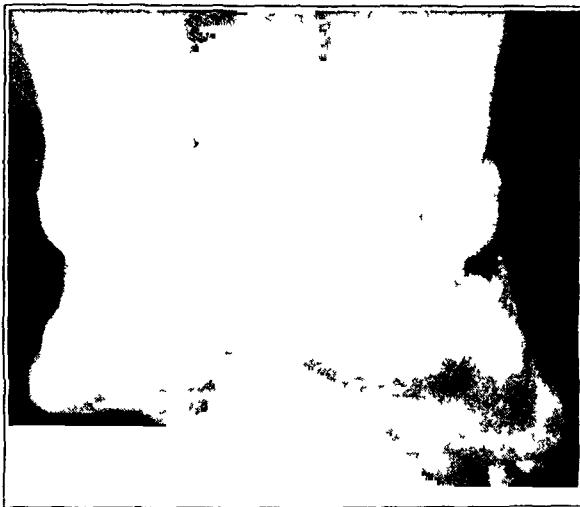


Fig 3 (case 1) —Xanthoma tuberosum of the achilles tendons

The real cause of xanthomatosis and other forms of lipoidosis is not known, in fact, an understanding of this group of diseases is in its early stages. It is believed that the lipoids are deposited in the cells of the reticuloendothelial system.



Fig 4 (case 14) —Xanthoma tuberosum. In this case there was just one small node, it was on the extensor tendon of the middle finger.

REPORT OF CASES

The patients came from seventeen families. The members of these families who appeared to have been or to be affected by xanthomatosis, 76 in all, have been grouped as follows



Fig 5 (case 32) —Xanthoma tuberosum



Fig 6 (case 5) —Xanthoma tuberosum of the achilles tendons

(a) The families in which xanthoma tuberosum, eventually also palpebral xanthelasma, occurred

(b) The families in which palpebral xanthelasma occurred

(c) The families in which there were no changes in the skin or subcutaneous tissue but in which the cardiovascular disease occurred in combination with hypercholesteremia and in which postmortem observations or other factors suggested that xanthomatosis might be the main cause of the cardiovascular disease

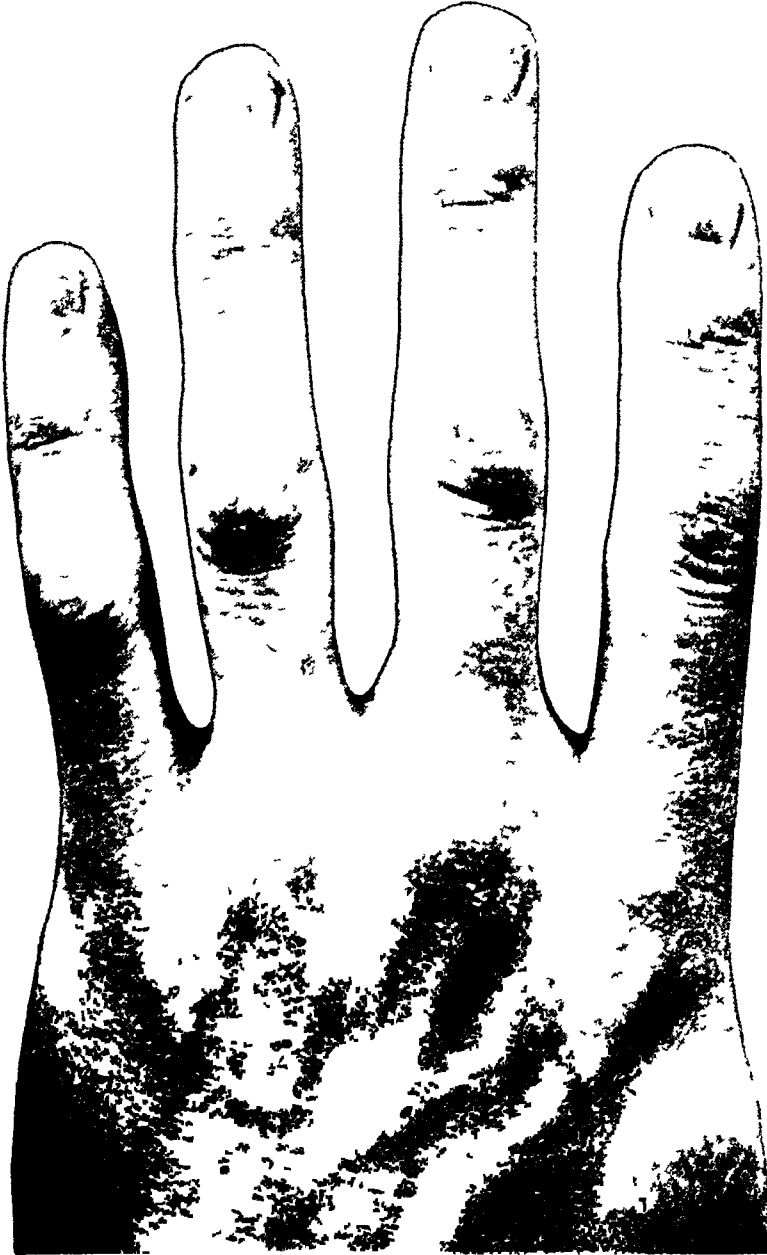


Fig 7—Garrod's pads—fibrous nodules over the joints between the first and the second phalanges of the second and fifth fingers. These pads are hereditary.

Genetic charts are presented of families, many members of which have been studied (fig 8)

Determination of the cholesterol content of the blood was made according to the Liebermann-Burchard colorimetric method as modified by A. Folling. The normal limits are 100 to 200 mg per hundred cubic centimeters. In every case duplicate analyses were made.

Families with Xanthoma Tuberosum and Angina Pectoris, Eventually Also Palpebral Xanthelasma—FAMILY 1 (fig 9)—A man (case 1) aged 45, an office worker, was admitted on April 13, 1937. When about 30 years old he noticed

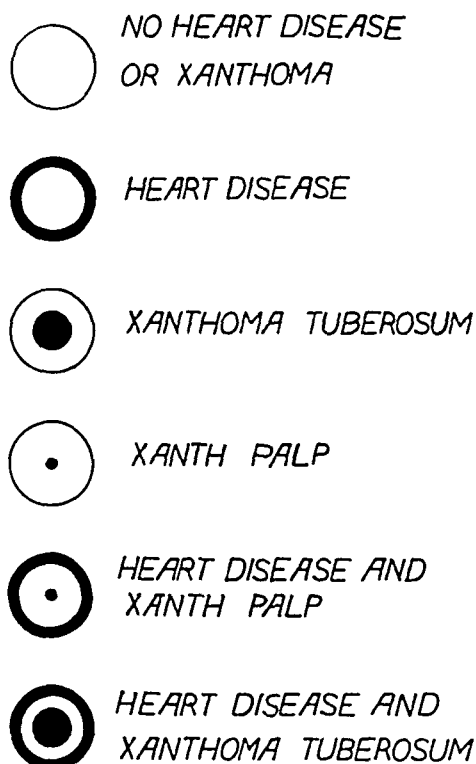


Fig 8—Key to the symbols employed in the following charts

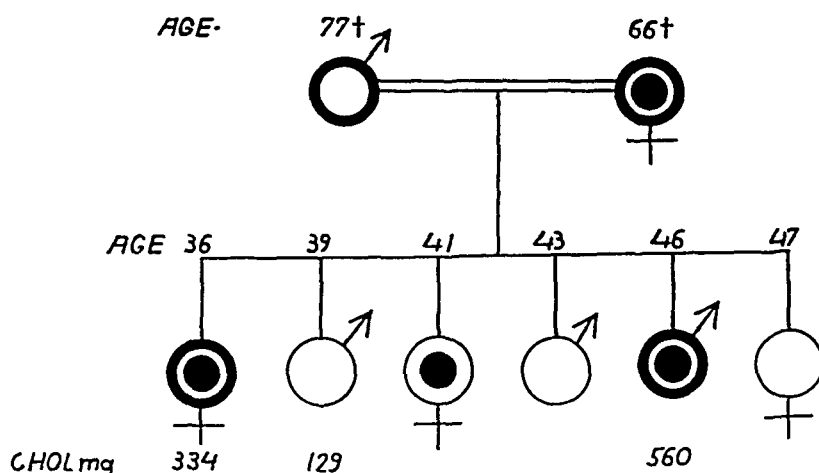


Fig 9—Family 1

tender nodules on the dorsum of several fingers, on the elbows under the patellar ligament and on the achilles tendons (fig 3). The nodules, almost symmetrically located, increased in size slowly and caused no disturbance except cosmetically. In 1932 a nodule was removed from the back of one finger, and microscopic sections revealed xanthomatous tissue. During the past ten years he had had

dyspnea on exertion and more recently typical attacks of angina pectoris, the pain stopping with rest or after the taking of glyceryl trimtrate. The electrocardiogram showed flattened T_1 and T_2 waves after exertion. In 1932 the blood content of cholesterol was 331 mg per hundred cubic centimeters, in April 1937 it was 560 mg per hundred cubic centimeters. The blood pressure was 125 systolic and 75 diastolic. The Wassermann reaction was negative. Roentgenographically the heart, the skull and the extremities were normal.

The patient's father and mother died of angina pectoris at the ages of 77 and 66 years, respectively. The mother (case 2) had nodules on the hands. Of the 5 siblings, 1 sister (case 3) 36 years old had the same cardiac symptoms on exertion as the patient. Examination of the heart and the electrocardiogram revealed no abnormality. Since her twenty-first year she had observed nodules, first on the heels and then on the elbows, under both knee joints and on the back of the second and third fingers of both hands. The cholesterol content of the blood was 334 mg per hundred cubic centimeters. A second sister (case 4) had nodules on both heels but was otherwise well. The other siblings seemed well.

Comment—A 45 year old man and his sister aged 36 years both suffered from angina pectoris with hypercholesteremia. A second sister had xanthoma tuberosum. The father and mother both died of angina pectoris, the mother had nodules on the hands.

FAMILY 2—The first patient (case 5) in this family was a 76 year old man, an architect. I saw him first in 1935 on account of angina pectoris, from which he had suffered in increasing degree for sixteen years. At that time I did not associate the xanthomas, which he had had for forty years, with the angina. The blood contained 304 mg of cholesterol per hundred cubic centimeters. The patient died of angina pectoris in June 1937. The xanthomas, which had grown slowly in the course of years, were unusually large (fig. 6).

This patient had 3 brothers and 7 half siblings on the father's side, all of whom were well except 1 full brother (case 6) 73 years old who had suffered from typical angina pectoris during the past six years. For about thirty years he had had nodules located much like those in case 5 but smaller. The cholesterol content of the blood was 440 mg per hundred cubic centimeters. The heart was normal. The blood pressure was 150 systolic and 100 diastolic. The patient had 5 children, 1 of whom, a son (case 7) 39 years old, had complained of cardiac symptoms, but examination revealed only barely demonstrable thickenings over the terminal joints of the second and third fingers. The blood was not examined for cholesterol.

The first patient in this family (case 5) had 2 sons and 1 daughter. One son (case 8) had xanthoma tuberosum at both tibial tuberosities, and the daughter (case 9) had small xanthomatous nodules at the tibial tuberosities and on the dorsum of both long fingers. The sister showed a cholesterol content of the blood of 350 mg per hundred cubic centimeters. Recently reports have been received to the effect that the second son has xanthoma nodules like those of his brother (case 8). The father (case 10) of 2 of the patients (cases 5 and 6) had larger nodes on the hands (about like those in case 5) and died of angina pectoris at the age of 58 years.

Comment—A man 76 years old with xanthoma tuberosum and xanthomatosis died of angina pectoris about sixteen years after the disorders

were first noted. His father had xanthoma tuberosum and also died of angina pectoris. A son 41 years old and a daughter 36 years old both had xanthoma, the daughter showed hypercholesteremia (350 mg of cholesterol per hundred cubic centimeters). A brother 73 years old had xanthoma, hypercholesteremia (440 mg of cholesterol per hundred cubic centimeters) and angina pectoris, and his son had doubtful xanthoma nodules and mild anginal symptoms.

FAMILY 3—A man (case 11) aged 59 years, a warehouse manager, had had symptoms of angina pectoris since his forty-eighth year. These were still quite typical after exertion. The blood pressure was 160 systolic and 115 diastolic. The heart was hypertrophic. The cholesterol content of the blood was 386 mg per hundred cubic centimeters. Xanthoma nodules were present on the fingers, the

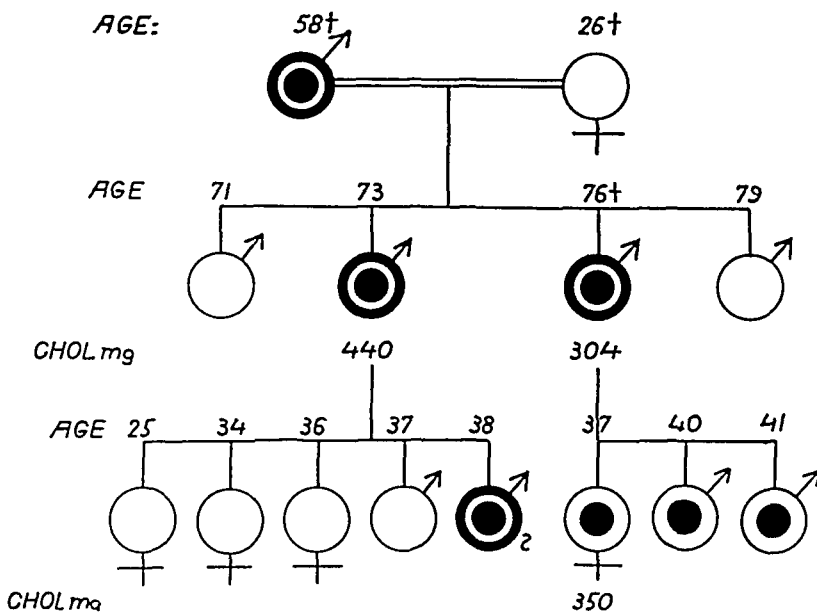


Fig 10—Family 2

left olecranon, the tibial tuberosities and the achilles tendons. A photograph of his mother (case 12), who died in her seventy-third year, showed typical nodules on the hands. For several years before she died she had had pains in the chest.

FAMILY 4 (fig 11)—A woman (case 13) aged 67, a widow, had had pain in the cardiac region on exertion for more than ten years. In 1937 the blood pressure was 185 systolic and 100 diastolic. There was a systolic murmur over the apex of the heart. Extrasystoles were noted. The electrocardiogram indicated a pathologic condition. For seventy-two hours before admission to the hospital on Jan 4, 1938, she had suffered severe pain in the chest, and on entry the condition was typical of cardiac infarct with collapse (blood pressure, 110 systolic and 72 diastolic). The blood contained 262 mg of cholesterol per hundred cubic centimeters. Xanthelasma were present on all the eyelids (fig 1), and xanthoma nodules were present on the fingers, the tibial tuberosities (fig 12) and the heels. The patient died after a week. At autopsy (Dr E Waaler) yellow nodules were noted at the sites just mentioned. The heart weighed 620 Gm. The

valves were normal. The coronary arteries were everywhere sclerotic, with yellow spots and plaques, in the circumflex branch of the right coronary artery, about 4 cm

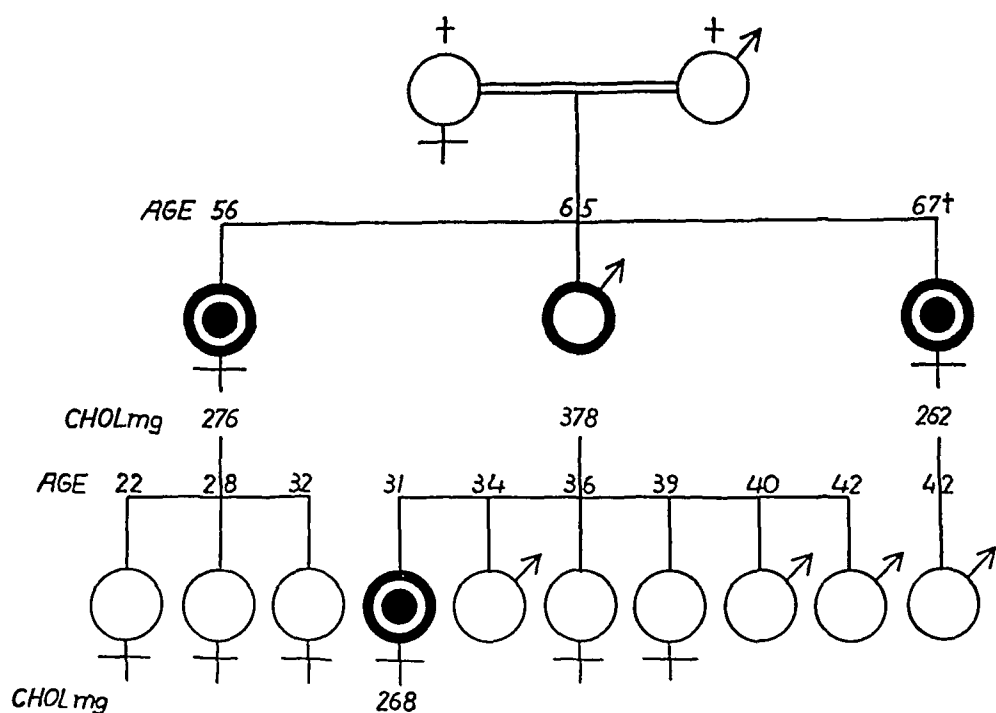


Fig 11—Family 4



Fig 12 (case 13)—A xanthomatous node below the knee. It was hard and might easily have been mistaken for an enlarged tibial tuberosity

from its origin, was a thrombus. The posterior wall of the left ventricle was the seat of an infarct, about 6 by 4 cm in size, with hemorrhagic borders. The aorta was markedly atherosclerotic (fig 13), and the pulmonary artery showed yellow deposits (fig 14). Xanthomatous deposits were present in the upper part of the

small intestine, being pea-sized yellow raised spots In the left kidney was a well circumscribed hypernephroma

The patient's father died at an early age of "inflammation of the bowels," and her mother died of cancer of the stomach The patient's son, aged 42 years, was in

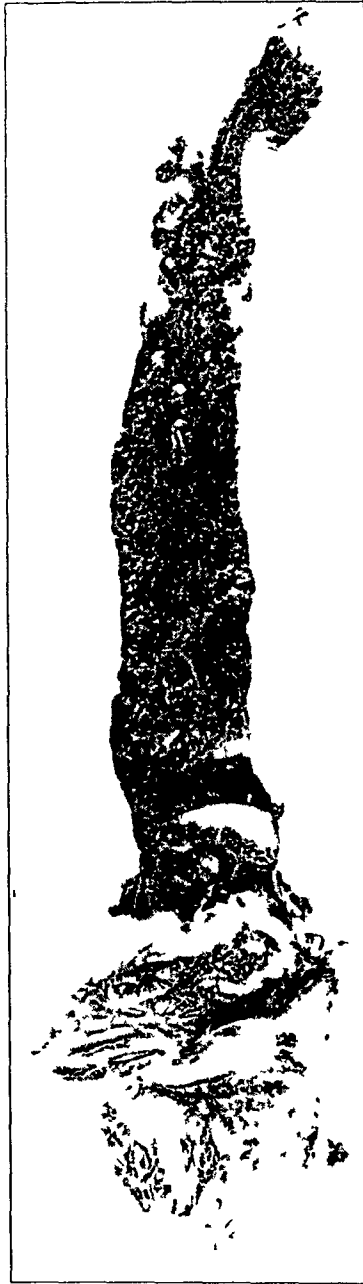


Fig 13 (case 13) —The aorta

good health, but her sister (case 14) and her brother (case 15) were not The sister, aged 56 years, had had anginal symptoms for many years An attack of rheumatic fever in 1925 had left no obvious effects on the heart On the back of the left hand was a xanthoma tuberosum (fig 4) The cholesterol content of the blood was 276 mg per hundred cubic centimeters The electrocardiographic

changes in this case greatly resembled those in case 13. In both cases ST_1 and especially ST_2 were deflected below the isoelectric line, and there were extrasystoles of the same type. The patient had 3 daughters (22, 28 and 32 years, respectively), the oldest one had "a nervous heart." The brother (case 15), 65 years of age, a coal dealer, had noticed for many years that he became short of breath when climbing a hill or stairs but was otherwise in good health until October 1937, when he had a severe attack of pain in the region of the heart lasting about twelve hours. Since then he had had pains in the elbows and in the chest on walking. There was no external evidence of xanthomatous deposits. On Sept 16, 1938, the cholesterol content of the blood was 378 mg per hundred cubic centimeters. Over the lower part of the sternum there was a systolic murmur. The blood pressure was 140 systolic and 110 diastolic. The electrocardiogram was abnormal.

The patient had 6 children, all apparently well save the youngest, a married woman 31 years old (case 16), who gave a ten year history of attacks of pain in



Fig 14 (case 13) —Whitish yellow spots in the pulmonary artery

the cardiac region, radiating into the back only. There was no dyspnea. Glyceryl trinitrate was reported to relieve the pain. Four years before, during pregnancy, a xanthelasma appeared on the left upper eyelid and a xanthomatous nodule on the back of the right hand. The blood pressure was 125 systolic and 85 diastolic. There was no enlargement of the heart, and the electrocardiogram was abnormal. On September 16 the blood contained 268 mg per hundred cubic centimeters of cholesterol.

Comment—Two sisters 67 and 56 years of age, respectively, and a brother 65 years old had angina pectoris and hypercholesteremia (262, 276 and 378 mg of cholesterol per hundred cubic centimeters, respectively). The sisters had xanthoma tuberosum, and the elder one had palpebral xanthelasma. This sister, who had hypertension, died of cardiac infarction. There was extensive atherosclerosis of the aorta and of the pulmonary artery, there were also xanthomatous nodules in the

small intestine. The brother, who showed no signs of external xanthomatosis, had 6 children. One daughter, 31 years old, presented xanthelasma on the left eyelid, xanthoma tuberosum on the right hand and hypercholesteremia (286 mg of cholesterol per hundred cubic centimeters). For about ten years she had had cardiac pain on exertion. The most remarkable feature of the disorder in this family seemed to be that the highest cholesterol content of the blood was found in the patient who had no changes in the skin.

FAMILY 5—A man (case 17) aged 51, a shipping agent, had pneumonia in 1917 and icterus and nephritis eight or ten years before entry. He had rheumatic fever four or five times between 1911 and 1930. For many years he had had nodules on the hands, elbows, knees, heels and eyelids (fig 2). Repeated efforts had been made to remove the palpebral deposits, but they had always returned. During

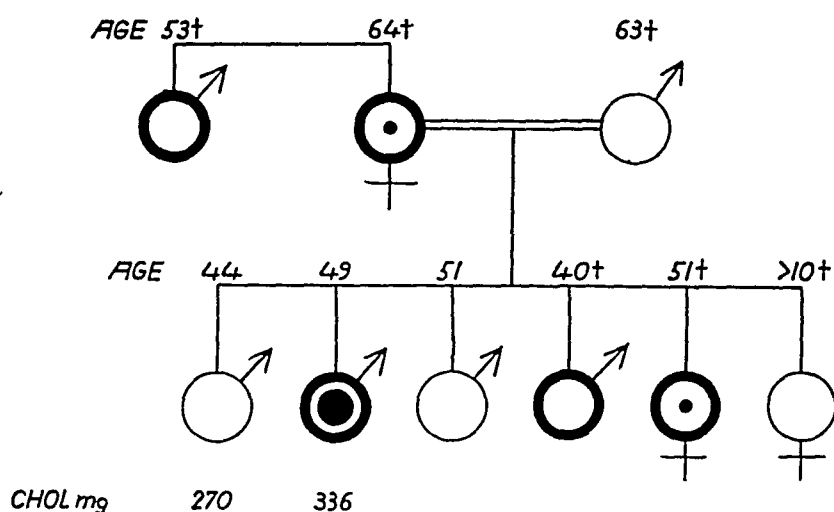


Fig 15—Family 6

the last ten years he had had palpitation and dyspnea on walking and in the course of the last three months precordial pains radiating to the left arm. The pain came on only on walking and disappeared when he remained quiet or took glyceryl trinitrate. On June 6, 1938, the blood pressure was 130 systolic and 90 diastolic. There was no enlargement of the heart. A weak systolic murmur was heard over the apex, the electrocardiogram was abnormal. The cholesterol content of the blood was 435 mg per hundred cubic centimeters. There were large, intensely yellow xanthelasmas on both lower eyelids and xanthomas of varying consistencies on the fingers and elbows, about the knees anteriorly, on the achilles tendons and along the dorsum of each foot. There was no history of xanthomatosis in these cases. Of the 3 siblings, a sister (case 18) has xanthelasma of the eyelids, but whether she has nodules elsewhere is not known.

FAMILY 6 (fig 15)—A man (case 19) aged 49, an agent, suffered with a gastric ulcer from 1920 to 1922 but was otherwise well until eight or ten years before entry, when exertion was followed by constricting pain across the chest and into the arms which subsided with rest. These attacks had become worse, and he

had had to give up rowing, sking and other activities and had had to move slowly even on flat ground. On Sept 26, 1938, the blood cholesterol value was 336 mg per hundred cubic centimeters. The electrocardiogram was abnormal (infarction). The right upper eyelid showed a small yellow deposit, the right hand a small thickening on the back, and the tibial tuberosities typical xanthomas.

In her last years the patient's mother (case 20) had cardiac pains and dyspnea. There is reason to believe that she had palpebral xanthelasma. She died at 63 of heart disease. She had 3 brothers and 3 sisters. Two of the brothers were well, the younger one (case 21), 44 years of age, was examined, the blood cholesterol value was 270 mg per hundred cubic centimeters. The third brother (case 22) died suddenly at 40 years of age, he had suffered from angina pectoris, but whether he had xanthelasma or xanthoma is not known. There was a positive reaction to the Wassermann test of the blood. One sister (case 23) died suddenly in 1937, at the age of 51 years, after having had clinically typical angina pectoris for some time. She also had xanthelasma on all the eyelids. Prof H Salvesen had charge of the two last-mentioned patients (cases 22 and 23) and found that both had typical angina pectoris without hypertension, physical examination of the heart revealing no abnormality.

The uncle (case 24) on the mother's side of 1 patient (case 19) was 53 years old when he died suddenly while sitting in an automobile.

Comment—A man aged 49 years with xanthoma tuberosum and hypercholesteremia (336 mg of cholesterol per hundred cubic centimeters) had angina pectoris. His mother had died at the age of 64 of heart disease and had had palpebral xanthelasma. A brother and a sister of the patient both died suddenly, at 49 and 51 years, respectively, after having had angina for several years. The sister had extensive palpebral xanthelasma. The patient's maternal uncle also died suddenly. One of the patient's brothers, 44 years old, has cholesteremia.

FAMILY 7—A married woman (case 25) aged 38 was referred to me by Dr Scott Mathiesen, who had removed xanthelasmas from her eyelid. These appeared in January 1937 after a cold. There was a soft nodule about the size of a hazelnut on each achilles tendon. She had rheumatic fever in 1935, the heart did not seem to be affected. I examined her on May 24, 1938. She said she felt well, became a little short of breath on exertion but went swimming, cycling and sking. There was a weak systolic murmur at the apex of the heart. There was no enlargement. The electrocardiogram was normal. The blood pressure was 120 systolic and 80 diastolic. The cholesterol value of the blood was 500 mg per hundred cubic centimeters. On September 20 she consulted me again. Early in July an attack of severe pain in the chest set in as she was cycling homeward in a hurry on account of rain. After that she had similar but less acute pain after much less severe exertion. The pains had not radiated into the arms. The heart seemed normal. The blood pressure was 120 systolic and 65 diastolic. The cholesterol value of the blood was 438 mg per hundred cubic centimeters. The palpebral xanthelasmas had returned. Her 4 children, 8 to 18 years old, were all well. Of her 4 siblings, 2 had died (pneumonia and brain tumor, respectively), and 2 were well. Her father, a physician aged 76, had had angina pectoris since about the age of 60, her mother (case 26) had died suddenly on the street, having had angina pectoris during the previous year, she was said to have had palpebral xanthelasma. The patient's grandmother (case 27) died suddenly of heart disease at the age of 57.

FAMILY 8 (fig 16)—An unmarried woman (case 28) aged 42, an office assistant, was referred to me by Dr Scott Mathiesen. She had influenza in 1918 and anemia with achylia gastrica in 1922. In 1923 a physician found that she had heart disease, but there were no special symptoms until in February 1938, when attacks of pain in the cardiac region, radiating into the chest, the back of the neck and the top of the larynx, appeared when she was walking. The attacks ceased when she stopped walking and took glyceryl trinitrate. Xanthelasma palpebrarum was present, and there were also hard nodes at the tibial tuberosities. The blood pressure was 130 systolic and 90 diastolic. The area of cardiac dulness was increased, there were systolic and diastolic murmurs at the apex. The cholesterol value of the blood was 305 mg per hundred cubic centimeters. The patient had 3 living brothers and 1 sister, 36 to 42 years of age. One of the brothers (case 29), 41 years old, had had typical palpebral xanthelasmas which had disappeared spontaneously. The cholesterol value of the blood was 235 mg per hundred cubic

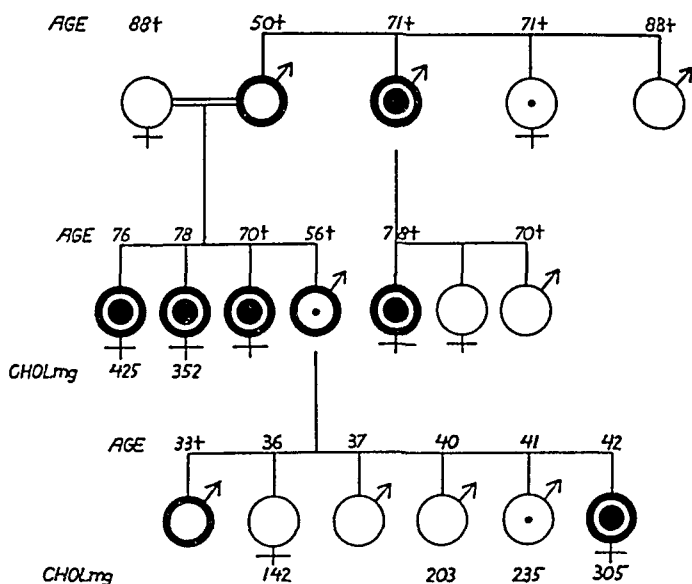


Fig 16—Family 8

centimeters. There were no signs of heart disease or xanthomatosis in the other brothers (1 had a cholesterol value of 203 mg per hundred cubic centimeters) or in the sister (the cholesterol value was 129 mg per hundred cubic centimeters). One brother (case 30) died at the age of 33 of heart disease, he had had rheumatic fever several times, and autopsy showed chronic rheumatic endocarditis and pericarditis as well as calcification of the mitral valves. I obtained this information from Dr R Hatlehol. The father (case 31) of these siblings died suddenly at 56 of angina pectoris. He had palpebral xanthelasma. Of his 3 sisters, the youngest (case 32) presented herself for examination. She was 76 years old and unmarried. Since about the age of 70 she had suffered from pain over the sternum and extending into the neck and both arms to the wrists. The pain came on with walking and especially soon after eating but disappeared with rest. Since about 45 years of age she had had palpebral xanthelasma and nodules on the back of the fingers (fig 5), elbows and heels. The nodules had grown slowly. The heart was apparently normal. The blood pressure was 150 systolic and 85 diastolic. The cholesterol value of the blood was 425 mg per hundred cubic

centimeters I had the opportunity of seeing the next youngest sister (case 33), aged 78 years. Six years previously she had herpes zoster in the left shoulder, otherwise she had enjoyed good health until about two years ago, when she began to have attacks of precordial pain when she walked or did heavy housework, but the pain disappeared with rest. The blood pressure was 150 systolic and 75 diastolic. The cholesterol value of the blood was 352 mg per hundred cubic centimeters. Xanthelasma of the lids was barely visible. There were xanthomatous deposits (noticed first when she was in her fifties) on the fingers, tibial tuberosities and achilles tendons. The heart was somewhat enlarged toward the left, and there was a systolic murmur over the apex.

The third sister (case 34), the oldest, died of heart disease at 70, having had pains in the chest, xanthelasmas and xanthomas.

The father of these 4 patients died suddenly when running to catch a train. He had 2 brothers and 1 sister. One brother, the oldest of the 3, died at 88, the cause being unknown. The next oldest (case 36), the sister, also died of unknown cause at 71, having had large palpebral xanthelasmas. The other brother (case 37) died at 71 suddenly on the way to his office, he had nodules on the hands as well as xanthelasmas. This brother had 3 children, but nothing is known about them except that the youngest, a daughter (case 38), died of heart disease at 78. Professor Harbitz, her physician, told me that she had extensive arteriosclerosis, large palpebral xanthelasmas and nodules on the hands.

Comment—In this family in three generations xanthomatosis and heart disease occurred in 7 persons, only xanthelasma in 2 and heart disease without any changes in the skin in 2. In the 9 cases of heart disease the indications were that angina pectoris occurred in 7, 3 patients dying suddenly. In 4 members with signs of xanthomatosis, hypercholesteremia was noted (235, 305, 352 and 425 mg of cholesterol per hundred cubic centimeters, respectively). In 2 others, who seemed to be well, the cholesterol values were 203 and 142 mg per hundred cubic centimeters, respectively.

Families with Palpebral Xanthelasma and Angina Pectoris—FAMILY 9—A widow (case 39) aged 64 had been well until February 1937, when she became dyspneic and felt pressure in the throat on walking up hill. A physician prescribed glyceryl trinitrate, which seemed to help her. On March 27, 1938, she suffered a severe attack of pain in the chest which lasted for two hours, with dyspnea. There was palpebral xanthelasma. The cholesterol value of the blood was 270 mg per hundred cubic centimeters. The electrocardiogram showed infarction of type "T₁", no enlargement of the heart or murmurs were noted. The patient died suddenly on Sept 2, 1938, without any marked change in her general condition. Her parents died of unknown causes, a sister aged 70 had diabetes, a brother aged 68 was well.

FAMILY 10—From 1928 to 1930 I had under my care a married woman (case 40) aged 55 years who had angina pectoris and xanthelasmas on all the eyelids. The angina began in February 1928, and the xanthelasmas were noticed first in 1922. She at present is under the care of Dr. Olaf Romcke, of Drammen, Norway, who has informed me that the xanthelasmas now surround both eyes and that the angina, which is alleviated by glyceryl trinitrate, remains about as in 1928. The cholesterol value of the blood in October 1938 was 454 mg per hundred cubic

centimeters In the electrocardiogram, T_1 was flattened and T_2 negative Of the patient's 6 siblings, 3 died while young, 1 boy died of heart disease at 14, a brother (case 41) died of heart disease at 60, the surviving brother (50 years old) is well The surviving sister (case 42), who is 53 years old, has xanthelasma about both eyes and anginal symptoms Her heart is apparently normal The cholesterol content of the blood was 535 mg per hundred cubic centimeters in October 1938 The mother (case 43) of these patients died at 54 of angina pectoris, she had palpebral xanthelasma

FAMILY 11 (fig 17) —A married woman (case 44) aged 68 was under my care for several years on account of angina pectoris In June 1937 she reported that she was worse I then noted xanthelasma on the upper left eyelid, this had been present at least thirty years About twenty-five years previously a similar spot

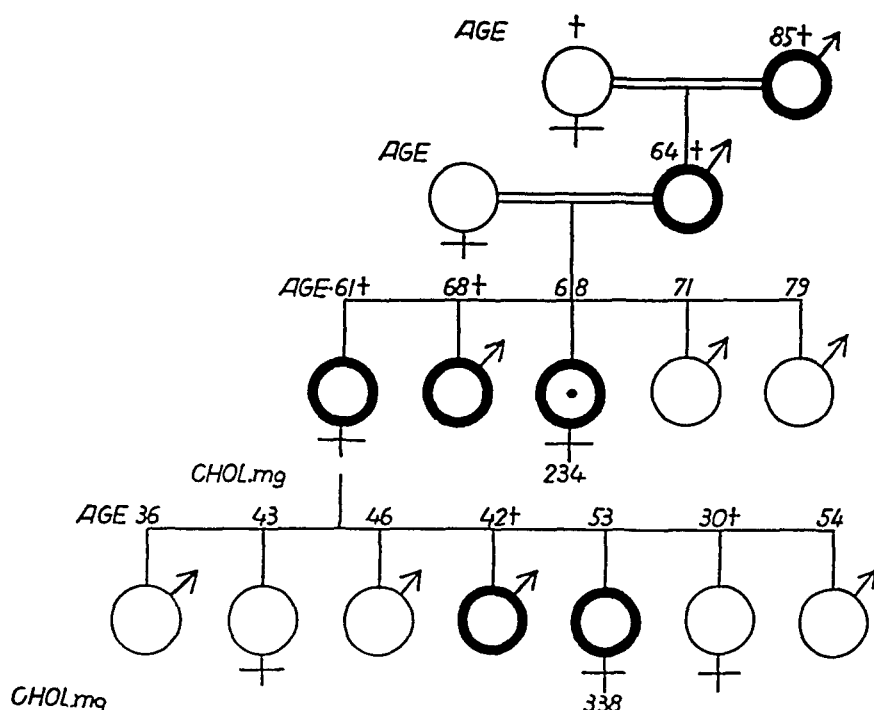


Fig 17—Family 11

had been removed from the right upper lid There were doubtful xanthomatous deposits on the fingers The blood pressure was 140 systolic and 95 diastolic The cholesterol content of the blood was 234 mg per hundred cubic centimeters The electrocardiogram suggested previous myocardial infarction

The paternal grandfather (case 45) and the father (case 46) died of angina pectoris, at 85 and 64 years of age, respectively, a sister (case 47) and a brother (case 48) also died of angina pectoris, at 61 and 68 years, respectively I treated the sister, who had anginal symptoms for many years and died of cardiac infarct I am unable to say whether she had any cutaneous deposits Her son (case 49) came under my observation a few years ago, he was then about 40 and complained of typical anginal symptoms, he died suddenly at the age of 42 The cause of the angina in this case was discussed with Dr Olaf Bang, who referred the patient to me, now, when the case is considered in the light of the family history, the cause seems plain enough Finally, the last patient had a sister (case 50), 53 years

old at the time of writing, who had presented signs of mitral stenosis since youth and more recently had possibly presented signs also of aortic stenosis, but without the history of any infectious disease as a basis. She has hypercholesteremia (338 mg of cholesterol per hundred cubic centimeters), there are no signs of xanthomatosis.

Comment—In four generations of this family there have occurred 7 instances of heart disease, mostly of angina pectoris. Two of these patients showed hypercholesteremia (234 and 338 mg of cholesterol per hundred cubic centimeters, respectively), and 1 had palpebral xanthelasma.

FAMILY 12 (fig 18)—Dr H G Dedichen referred to me a widow (case 51) 79 years old with aortic insufficiency, angina pectoris, hypertension, palpebral xanthelasma and hypercholesteremia (225 mg of cholesterol per hundred cubic

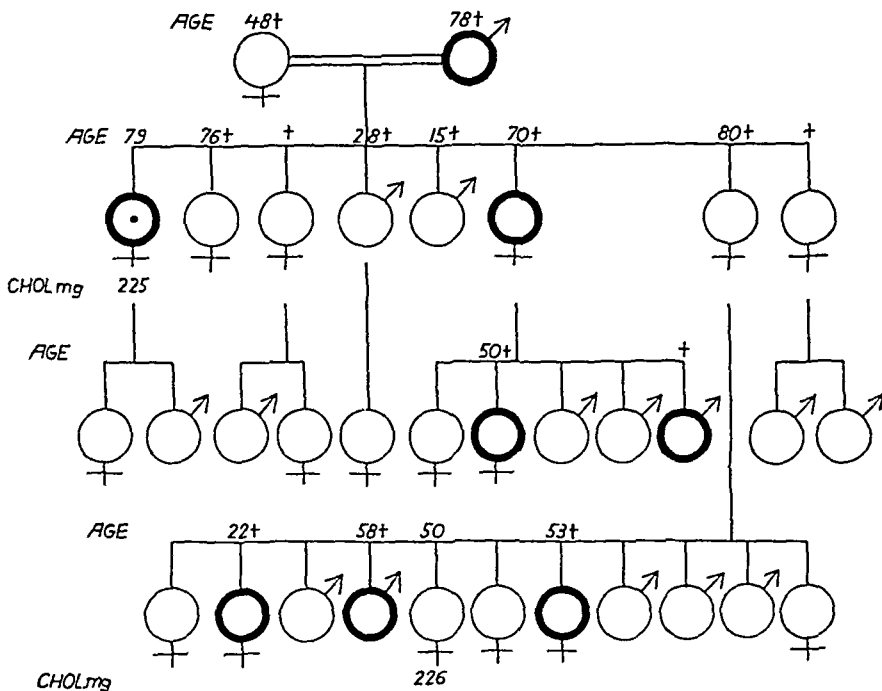


Fig 18—Family 12

centimeters). The electrocardiogram showed bundle branch block of the usual type. The Wassermann reaction was negative. She had rheumatic fever when 12 to 14 years old. In three generations of her family, 7 members died of heart disease, 4 of them suddenly. The father (case 52) died suddenly at the age of 78, the mother died of typhoid at 52, a sister (case 53) died suddenly at 70 of heart disease while sleeping, her daughter (case 54) aged 50 died on the street while on her way to her physician because she had pains in the cardiac region, and her son (case 55) died of cardiac disease.

The next oldest of the 6 sisters (case 51) died at 80 of unknown cause. She had 11 children, among them 2 daughters (cases 56 and 57) and a son (case 58) who died of heart disease at 22, 53 and 58 years, respectively. Of these siblings, 1 survivor is a woman aged 50 who has no cutaneous deposits or sign of heart disease. The cholesterol content of the blood is 226 mg per hundred cubic centimeters.

FAMILY 13—A married woman (case 59) 41 years old had yellow spots on all her eyelids which returned after being removed twice. She had had anginoid pains as long as she could remember but not typical angina pectoris. The heart appeared normal on examination, the cholesterol content of the blood was 270 mg per hundred cubic centimeters. Her mother (case 60) aged 65 complained of dyspnea and had to walk slowly. She had yellow spots on both upper lids. Her maternal uncle (case 61) died suddenly on the street at 65 years of age, 1 sister (case 62) died of heart disease at 52, her husband (case 19), not a blood relation, was a member of family 6.

FAMILY 14—A married woman (case 63) aged 55 had noticed a yellow spot on the right upper eyelid for two years, it appeared soon after an attack of biliary colic. For six years she had had dyspnea on exertion and a disturbed heart action. On Feb 19, 1938, a cerebral embolism caused paresis of the left side and difficulties of speech. On March 3 there was typical mitral stenosis with auricular fibrillation. The cholesterol content of the blood was 235 mg per hundred cubic centimeters. The electrocardiogram indicated a pathologic condition. There was no family history of heart disease or of xanthomatosis.

Families with Probable Xanthomatosis and Angina Pectoris Without Xanthoma or Xanthelasma—FAMILY 15—A man (case 64) aged 58 for about a year had had a burning sensation behind the sternum and a tender spot under the left clavicle, especially after physical exercise. In April 1927 the heart was normal, the blood pressure was 140 systolic and 90 diastolic, and the electrocardiogram showed infarction of "type T₁". The blood cholesterol was 300 mg per hundred cubic centimeters. He died after an automobile accident, with multiple cerebral hemorrhages, extensive atherosclerosis in the aorta (fig 19) and pulmonary arteries, and myocardial fibrosis (autopsy by Dr E Waaler). The patient's brother (case 65) aged 65 consulted me in April 1937 on account of pains in the chest for three years. Since 1914 he had been treated for syphilis. The Wassermann test gave a negative reaction. The blood pressure was 220 systolic and 110 diastolic. The cholesterol content of the blood was 263 mg per hundred cubic centimeters. There was accentuation of the second aortic sound. The electrocardiogram showed an abnormal condition. This patient's daughter (case 66) aged 35 was examined on Oct 1, 1938, and was found to have mitral stenosis and hypercholesteremia (338 mg of cholesterol per hundred cubic centimeters). A sister (case 67) of the 2 brothers died at 47 of heart disease associated with violent pain. There have been several cases of heart disease among relatives of the mother.

FAMILY 16—A married woman (case 68) aged 59 had transitory angina pectoris in her forty-seventh year, the symptoms reappearing in her fifty-seventh year, followed in about half a year by cardiac infarction (type T₁) and then signs of cerebral embolism. She continued to have angina on exertion, hypertension and hypercholesteremia (273 mg of cholesterol per hundred cubic centimeters). Both parents had cardiac symptoms, the mother (case 69) dying of angina pectoris, as did also the sister (case 70), at the age of 60, a second sister (case 71), who was 50 years old, had had symptoms like those of the patient. There was no history of xanthomatosis in the family.

FAMILY 17—Two brothers (cases 72 and 73) had cardiac infarction of type III at 44 and 38 years of age, respectively. Both had hypercholesteremia (300 and 214 mg of cholesterol per hundred cubic centimeters, respectively), as did also an insane sister (case 76), who otherwise seemed well (222 mg per hundred cubic centimeters). The mother (case 74) died of heart disease at 57 and the father (case 75) of heart disease with dropsy.

COMMENT

The foregoing histories deal with 76 persons (32 men and 44 women) of interest to the subject of this paper. I have myself examined 33 of

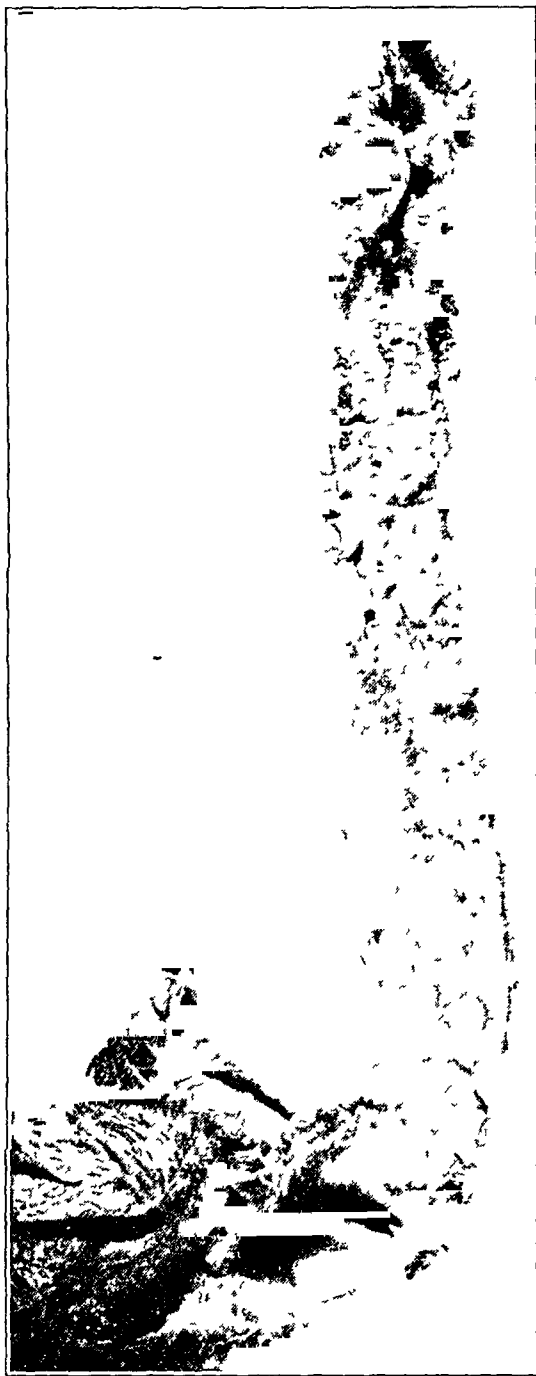


Fig 19 (case 64) —The aorta

these persons, concerning the rest I have given the information that I have obtained from others. The ages varied from 31 to 85 years, the average for the living members being 56.3 years and for the deceased ones 60.9 years. Most of these persons were office workers or teachers

The laboring class was not represented, in spite of the fact that most of my patients come from that class

Of the 76 persons, 68 appeared to have had heart disease, while 8 had xanthelasma only. Of the 68 persons, the diagnosis of angina pectoris seemed indicated in 59, of whom 38 have died, 14 suddenly, in 11 cases signs of cardiac infarction were found, and 3 of these persons have died. In 11 cases heart disease was reported but without information as to its nature, presumably 5 have had valvular lesions. In 6 of the 33 patients I examined hypertension (160 systolic or more) was found. Syphilis was mentioned in the history in 2 cases, but the Wassermann reaction was negative. No positive reaction to the Wassermann test was obtained, but the test was made in only a small number of cases. Five of the patients had had acute rheumatic fever, and in 1 case (case 30) death no doubt resulted from rheumatic carditis. Case 51 concerns a woman 79 years old who had rheumatic fever when 12 or 14 years old and now has signs of aortic insufficiency and typical angina pectoris. The 3 other patients who had had rheumatic fever had no valvular disease but showed signs of angina pectoris, presumably they did not have rheumatic heart disease.

In the seventeen family histories xanthoma tuberosum was noted alone or combined with xanthelasma in 8 families, in six families there were records of xanthelasma only, in 3 there were no records of cutaneous changes. Cutaneous xanthomatosis in one form or another occurred in 38 persons, xanthoma tuberosum in 24 and xanthelasma in only 14, 10 had both forms at the same time. Undoubtedly instances of xanthomatosis have been missed because the persons were not examined or because they were examined before I knew about its significance.

The quantity of cholesterol in the blood was estimated for 37 patients, the amount varied from 129 to 560 mg per hundred cubic centimeters. In all except 2 cases hypercholesteremia was found, and in these 2 cases there were no signs of xanthomatosis or heart disease. Of persons who had neither sign of heart trouble nor xanthomatosis, it was possible to obtain specimens of blood from only a small number, hence there is no way of knowing how many of the apparently well persons had hypercholesteremia and were hereditarily predisposed to it. The cholesterol content of the blood in the remaining 35 persons was as follows: Eight had 200 to 250 mg, 10, 251 to 300 mg, and 17, more than 301 mg, per hundred cubic centimeters. Hypercholesteremia, in some cases severe, consequently is commonly found. In 16 instances of xanthoma tuberosum, with or without xanthelasma, the average cholesterol content of the blood was 362 mg per hundred cubic centimeters, in 8 instances of xanthelasma only the average was 307 mg per hundred cubic centimeters and in 13 instances of external xanthomatosis the average was 256 mg per hundred cubic centimeters. Thus,

hypercholesteremia is most marked in connection with xanthoma tuberosum, but there seems not to be any definite relation between hypercholesteremia and deposits in the skin. In family 4, for instance, the highest content (378 mg) was obtained in case 15, in which there were no cutaneous changes, but for the patient's sisters (cases 13 and 14), both with xanthoma tuberosum, the values were lower—262 and 276 mg per hundred cubic centimeters, respectively. Neither does it appear that there is any definite relation between the cardiovascular changes and the degree of hypercholesteremia. Thus, for 7 persons who were apparently normal except for palpebral xanthelasma and whose family records showed no heart disease, the cholesterol content of the blood was 300 mg per hundred cubic centimeters. These patients are not included in my case reports.

The reports I have presented confirm the previous observations on xanthomatosis as a cause of hereditary heart disease. They reveal further that the syndrome of cutaneous xanthomatosis, hypercholesteremia and angina pectoris presents itself as a well defined clinical disease entity in the first, second, third and fourth generations, that is, as a dominant hereditary disease. There can be hardly any doubt but that xanthomatous deposits in the coronary artery and consecutive myocardial ischemia are the cause of the angina pectoris. That the disease may cause changes in the mitral and aortic valves is shown in earlier observations, both clinical and anatomic, as illustrated perhaps by cases 28, 50, 51, 63 and 66.

The case reports also show—and this is an important clinical observation—that the form of angina pectoris under discussion may occur in patients without external xanthomatosis. The data on families 4 and 11 illustrate that xanthomatosis may occur in a few members or only 1 member of a family, while relatives have heart disease and hypercholesteremia. I have listed also families 15, 16 and 17, in which external xanthomatosis was not demonstrated at all. In favor of xanthomatosis as the cause of heart disease in these three families were the hereditary occurrence and the hypercholesteremia. I wish to mention, too, the postmortem observations in case 64 (family 15), which resembled notably those in case 13 (family 4), in which xanthoma tuberosum was present.

Of great clinical interest is the observation that in xanthomatosis, angina pectoris not only may occur at an early age with sudden death but more often appears as typical angina pectoris, lasting for years in middle-aged as well as in old persons, that is, at the time this disease usually occurs at 60 to 70 years of age and even later. My reports also contain examples of the occurrence of angina at an earlier age, in 16 cases it commenced before the fiftieth year and in 8 of these between the thirty-first and the fortieth year.

Finally, my cases indicate clearly that xanthomatous heart disease is frequent. The case reports have been collected in the course of about one and one-half years and mainly in the course of my own practice. How many of the 68 cases of heart disease were due to xanthomatosis cannot be determined. That all were not due to xanthomatosis is presumably as certain as that many were. It is remarkable the small role which the usual causes of heart disease—rheumatic fever, syphilis and hypertension—appeared to play in these cases. Hypertension, which usually is regarded as a hereditary factor in heart disease, was encountered relatively infrequently and then usually in a mild form. At the same time it is to be noted that the diagnostic value of hypercholesteremia must not be exaggerated, because large or relatively large values are obtained in a number of conditions in spite of the fact that there is no essential xanthomatosis. But this reservation must not be assigned great importance. It should be mentioned that the cholesterol content of the blood in ordinary senile atherosclerosis, according to the recent investigations of Koch and Westphal,⁹ as a rule is normal (about 160 mg per hundred cubic centimeters in 7 of 8 cases, in 1 case being 260 mg). The hypercholesteremia demonstrated in hypertension is usually moderate and as a rule much lower than was the case in my material. Even if my experiences do not permit any final or definite statements about the frequency of the disease, they do leave the impression that it must be much more frequent than heretofore recognized. The frequency is illustrated by the fact that 1 of my families (family 13) was found by accident because a member (case 59) was married (but not related by blood) to a member of another family (case 19, family 6). The hereditary tendency to xanthomatosis and heart disease appears clearly established in both these families. That such instances have thus far been observed so infrequently may be variously explained. In the first place, the clinicians have not paid attention to the concurrence of the factors and conditions on which the diagnosis depends. Usually xanthelasma is regarded as an insignificant process and perhaps is not even noted in the case records, and both xanthelasma and xanthoma deposits may be so small as readily to escape observation. Determination of the cholesterol content of the blood is not carried out routinely in clinical practice, and in the case of heart disease, heredity is usually regarded as of little importance. The patients in question had no obvious external peculiarities characteristic of their condition, they all looked like ordinary persons. Usually the cardiac symptoms develop at the same age and are of the same kind as those of ordinary angina pectoris. It must be pointed out also that the anatomic changes in the heart and blood vessels are not distinctive and cannot be differentiated

9 Koch, K., and Westphal, K. *Deutsches Arch f klin Med* **181** 413, 1938

from common arteriosclerosis either grossly or microscopically. That pathogenically and etiologically distinct diseases, especially chronic disease, may lead to the same anatomic changes is illustrated by chronic nephritis and chronic arthritis. The hereditary occurrence of arteriosclerosis in xanthomatosis, the hypercholesteremia and the development of vascular disease early in life, even in children, indicate that a special form of arteriosclerosis is concerned which in any case has well marked clinical characteristics. The interesting question as to whether this xanthomatous form of arteriosclerosis can be differentiated anatomically from the senile form has not been discussed to any extent in previous communications. Harbitz,^{4b} however, has called attention to certain peculiarities of the xanthomatous form. Microscopically he found that the so-called foam cells are more marked and more characteristic than in senile arteriosclerosis. Macroscopically the deposits are intensely yellow, are more circumscribed, are irregularly distributed and are often in the form of nodes or clumps which may become large enough to obstruct the circulation. In ordinary arteriosclerosis the changes are said to be more diffuse. The changes in my cases 13 and 64 were, however, quite diffuse, in both cases the aorta and its large branches as well as the pulmonary artery were involved. The intimal deposits were markedly yellow. In case 13 there was considerable calcification, which was almost absent in case 34 (figs 13 and 19). The question of the identity of the arteriosclerosis in xanthomatosis with senile arteriosclerosis requires further study.

It is noteworthy that in xanthomatosis the vascular changes so frequently manifest themselves clinically in coronary disease and angina pectoris. In such a "system disease" one would expect also that other localizations, first of all the cerebral arteries, would cause symptoms. In my series there was only 1 death from apoplexy (case 64, family 15), and this patient had at the same time cardiac infarction. It may be that the coronary arteries do suffer earlier and more than other arteries or that lesions in the coronary arteries give rise more readily to symptoms. In this matter also further investigation is needed.

The treatment of the cardiac symptoms in xanthomatosis differs in no point from the treatment of cardiac symptoms under other conditions. The patients are benefited by quiet, rest in bed and nitrites. Is there a causal therapy? Xanthoma disseminatum diabeticorum may disappear on treatment with insulin and appropriate diet. It has been shown that the cholesterol content of the blood can be reduced by a diet poor in cholesterol. Koch and Westphal⁹ obtained the same effect with thyroid preparations. I have ordered a diet poor in cholesterol (no yolk of egg, butter, cream, fat milk or animal fat in general) and thyroid

tablets, but I have not been able to formulate any opinion in regard to the effects. The treatment may be of prophylactic value to persons with a hereditary predisposition.

SUMMARY

Hereditary heart disease due to xanthomatosis is fairly common. It is believed to have been demonstrated as a dominant factor in seventeen families. Xanthomatosis gives rise to a special form of arteriosclerosis which is etiologically and, consequently, clinically different from ordinary arteriosclerosis. It is possible that it may be different anatomically, too. Xanthomatous deposits may cause valvular lesions, but far more commonly the changes are in the coronary arteries, with angina pectoris. This may occur in young but more frequently in middle-aged and old persons. Symptomatically this form of angina pectoris does not differ from the usual form. In addition to chronic and long-continued heart disease, the condition may cause sudden death. Infarction of the myocardium is also a frequent result. Hypercholesteremia is present, most marked in connection with xanthoma tuberosum, but there is no definite relation between hypercholesteremia and xanthomatous deposits in the skin. Xanthomatous cardiac lesions probably may develop in persons who have no evidence of xanthomatosis in the skin. Xanthoma tuberosum and xanthelasma may be overlooked in clinical examinations and may be confused with other cutaneous conditions also. The occurrence of heart disease in families should direct the attention to xanthomatosis, especially when rheumatic fever, syphilis or hypertension does not appear to play any role. In the cases here reported, hypertension was infrequent. Finally, it seems possible that causal and prophylactic treatment may prove to be of value.

CHRONIC LEUKEMIA

THE EARLY PHASE OF CHRONIC LEUKEMIA, THE RESULTS
OF TREATMENT AND THE EFFECTS OF COMPLICATING
INFECTIONS, A STUDY OF EIGHTY-SIX ADULTS

MAXWELL M WINTROBE, M D

AND

L LEE HASENBUSH, M D

BALTIMORE

The opportunity to observe the course of chronic leukemia from a time before the disease has caused symptoms is necessarily rare, and few accounts of such opportunities are available in the literature. For this reason we have thought it worth while to describe several cases of very early leukemia which we have studied and to review the available information concerning the course of this disease.

An analysis of the cases of chronic leukemia in patients treated at the Johns Hopkins Hospital was also prompted by the frequently made statement that patients suffering from leukemia may, under the influence of infection, exhibit a reversal from a frankly leukemic picture to one closely simulating the blood picture of normal persons and that other manifestations of a remission may appear at the same time. This statement has been repeated so often that the impression is current that it is common for infections to cause a remission in chronic leukemia. Our own experience is quite to the contrary.

Finally, because of the recent renewal of interest in arsenical therapy, a brief account is given of the comparative effectiveness of irradiation and of potassium arsenite in the treatment of leukemia, and the relative responsiveness to therapy of the myelogenous and lymphogenous types of the disease is discussed.

MATERIAL

All cases of chronic leukemia in adults who were observed at this hospital between January 1926 and August 1938, inclusive, are included in this report. Two thirds of the patients were personally studied by one of us (M M W), and full data regarding the others were available in the hospital records. Many of the patients were observed at this hospital continuously or at intervals during their illness, and by correspondence with the patients, their relatives, friends or private physicians, the subsequent course in a number of the other cases was ascertained.

From the Department of Medicine, Johns Hopkins University, and the Medical Clinic, Johns Hopkins Hospital

The diagnosis of leukemia was carefully reconsidered in each instance, and only those cases are included which clearly meet generally recognized diagnostic criteria. The series includes 39 cases of myelogenous and 47 cases of lymphogenous leukemia. Autopsies were made in 28 cases, 14 of each type. Fifteen patients are still alive. Seven of the 39 patients with myelogenous leukemia and 8 of the 47 with lymphogenous leukemia were Negroes.

SEX AND AGE INCIDENCE

Of the patients with myelogenous leukemia, 24 (61.5 per cent) were males. This sex incidence corresponds almost exactly with that in the 605 cases collected from reports in the literature, as well as that in the experience of Minot, Buckman and Isaacs¹ and in the 180 cases reviewed recently by Leavell,² in both of which groups the proportion of males was 60 per cent. Of the 82 patients reported on by Hoffman and Craver,³ 68 per cent were males.

Thirty-nine (83 per cent) of our patients with chronic lymphogenous leukemia were men. The relatively high incidence of this type of leukemia in the male sex is well recognized. Seventy-five per cent of Ward's⁴ 84 patients, 74 per cent of the 92 patients reported on by Minot and Isaacs⁵ and 72 per cent of Leavell's² 128 patients were males.

In agreement with the observations of many writers, the age at onset was earlier in those with myelogenous than in those with lymphogenous leukemia (chart 1). In the total of 675 cases reported by Ward,⁴ Minot, Buckman and Isaacs,¹ Hoffman and Craver³ and Leavell,² the age at the onset of symptoms was most frequently between 30 and 50 years, and the decade in which the disease was most common was 35 to 45 years. Rosenthal and Harris⁶ have given 30 to 39 years as the decade of greatest incidence. In 30.8 per cent of our patients, symptoms first developed at this age, and in 72 per cent the age at onset was between 30 and 59 years.

1 Minot, G. R., Buckman, T. E., and Isaacs, R. Chronic Myelogenous Leukemia. Age Incidence, Duration, and Benefit Derived from Irradiation, *J. A. M. A.* **82** 1489 (May 10) 1924.

2 Leavell, B. S. Chronic Leukemia. A Study of the Incidence and Factors Influencing the Duration of Life, *Am. J. M. Sc.* **196** 329, 1938.

3 Hoffman, W. J., and Craver, L. F. Chronic Myelogenous Leukemia. Value of Irradiation and Its Effect on the Duration of Life, *J. A. M. A.* **97** 836 (Sept. 19) 1931.

4 Ward, G. The Infection Theory of Acute Leukemia, *Brit. J. Child. Dis.* **14** 10, 1917.

5 Minot, G. R., and Isaacs, R. Lymphatic Leukemia. Age Incidence, Duration and Benefit Derived from Irradiation, *Boston M. & S. J.* **191** 1, 1924.

6 Rosenthal, N., and Harris, W. Leukemia. Its Diagnosis and Treatment, *J. A. M. A.* **104** 702 (March 2) 1935.

In the cases of chronic lymphogenous leukemia, on the other hand, the decade in which the disease was encountered most often was 60 to 69 years, and in 61.7 per cent of the cases symptoms began between the ages of 50 and 69 years. Again our data are in somewhat better agreement with those of Rosenthal and Harris,⁶ who observed this disease most frequently in patients between the ages of 50 and 69, than with those of Waid,⁴ Minot and Isaacs⁵ and Leavell,² who found the greatest number of cases in patients between the ages of 45 and 54.

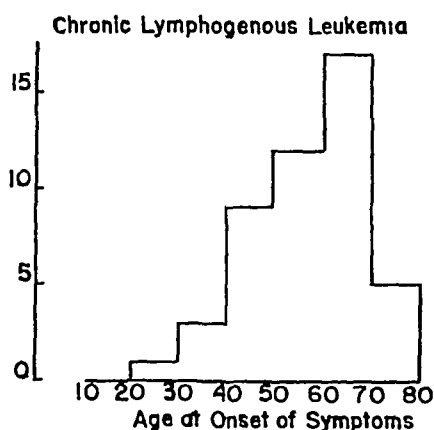
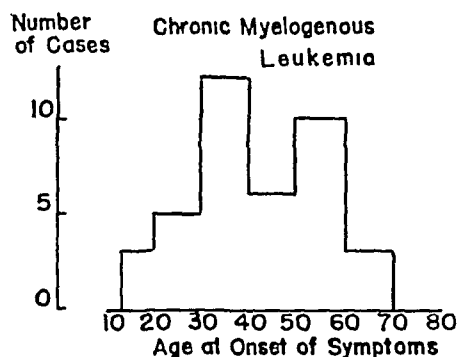


Chart 1 —The age at the onset of symptoms in 39 cases of chronic myelogenous leukemia and in 47 cases of chronic lymphogenous leukemia

EARLY PHASE OF CHRONIC LEUKEMIA

Because of the insidious character of this disease, it is usually recognized for the first time after widespread anatomic and physiologic abnormalities have developed. As already stated, we have had the opportunity to observe a number of patients from a time when symptoms and signs as well as changes in the blood were minimal or totally lacking until death occurred and autopsy confirmed the diagnosis, or at least until the clinical picture became so characteristic that there was little doubt about the correctness of the diagnosis.

Chronic Myelogenous Leukemia—In 3 patients who subsequently showed the typical clinical picture of chronic myelogenous leukemia, unexplained leukocytosis was found in the course of routine examinations following pregnancy in 1 case, for sterility in another and because of symptoms suggestive of disease of the gallbladder in the third. All 3 were young adults (28, 29 and 28 years of age, respectively). In the first patient (M J, chart 2) the spleen was found to extend about 2 cm. below the costal margin, the liver was just palpable and there was slight glandular enlargement in the axillas and groin. However, there was no anemia, and the leukocytes numbered only 28,000, of which 6 per cent were myelocytes and a total of 82 per cent were

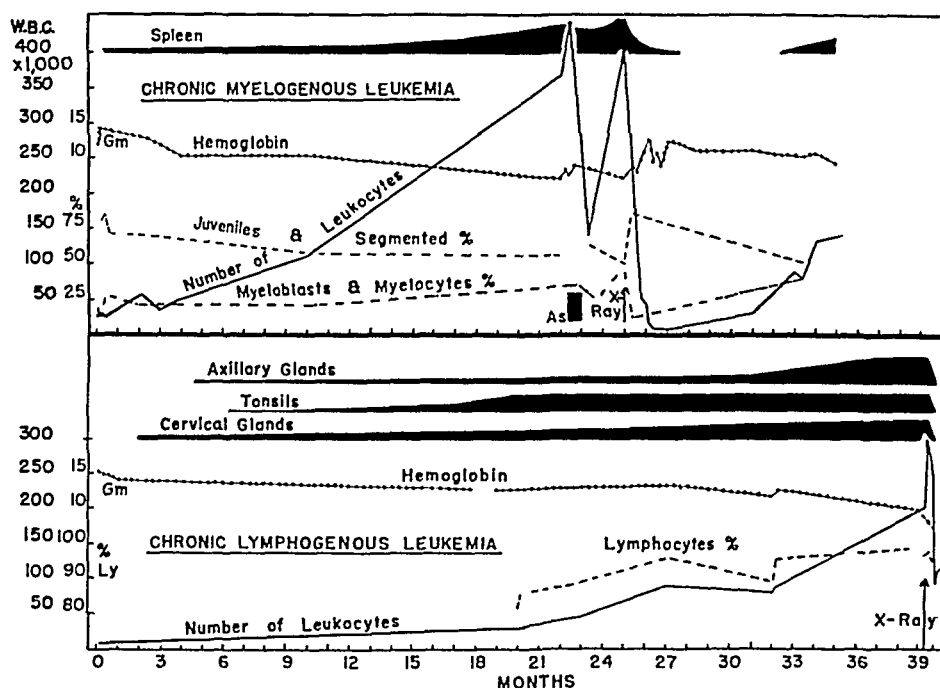


Chart 2—Diagrammatic presentation of the data in a case (M J) of chronic myelogenous leukemia and in a case (H V) of chronic lymphogenous leukemia. In each case the disease was discovered early in its course. The initial sign in the case of myelogenous leukemia was unexplained leukocytosis, that in the case of lymphogenous leukemia was glandular enlargement.

As indicates treatment with solution of potassium arsenite U S P, arrows marked "x-ray" indicate when irradiation was given.

myeloid leukocytes. The platelets were very numerous (1,200,000). Slight anemia developed 4 months after the leukocytosis was discovered. Six months later the leukocyte count was 116,800 (myeloblasts, 1 per cent, myelocytes, 24 per cent). It was 22 months after leukocytosis was first discovered before it was thought advisable to give treatment. The leukocyte count at this time was 377,000 and the red blood cell

count 2,590,000, but there were no complaints. This patient is still symptomatically well and able to do her housework, 3 years after the discovery of leukemia.

The second patient (R. H. H.) showed a leukocyte count at the first examination of 77,000 (myeloblasts, 5 per cent, myelocytes, 25 per cent) and there was slight anemia (red blood cells, 4,200,000, hemoglobin 14.7 Gm.), but physical examination revealed no abnormality except for the presence of a few small lymph nodes in the neck. It was 25 years before he sought medical assistance because of weakness and increased fatigability. At that time the leukocytes numbered 337,000, and the red blood cell count was 2,860,000. This man has received roentgen irradiation recently and is still carrying on active executive work without interruption, 4 years after the discovery of the disease.

The patient whose complaints suggested disease of the gallbladder (J. S.) was found to be anemic (hemoglobin, 8.7 Gm., hypochromic anemia probably due to other causes) and unexplained leukocytosis (26,000 cells) was recorded. Eighty-five per cent of the leukocytes were segmented neutrophils, and 4 per cent were juvenile forms. Physical examination showed no abnormality at this time, and it was not until 3 years and 9 months later that the spleen was palpable. Four years and 2 months later, after delivery of a healthy child, the leukocyte count was found to be 95,800, the spleen, liver and a few lymph nodes were palpable. The red blood cell count was 2,860,000, but this could be attributed chiefly to excessive loss of blood at the time of delivery. The progress of the leukemia in this case has been unusually slow. The patient was recently admitted to the Johns Hopkins Hospital because of an incomplete abortion. At the last examination, 5 years and 4 months after the unexplained leukocytosis was discovered, the liver, spleen and lymph nodes were still only moderately enlarged, the erythrocyte count was 3,090,000 and the leukocytes numbered 92,900. She has had no treatment for leukemia and has carried on her housework except when interrupted by the aforementioned pregnancy and abortion.

A fourth patient (H. R., a man aged 62 years) complained of abdominal distress. There was no anemia, but the leukocytes numbered 20,000. It was not until 1 year later that the spleen and liver were palpable, the leukocytes numbered 80,000, with 5 per cent myeloblasts as well as 25 per cent myelocytes, and there was slight anemia (red blood cells, 4,100,000, hemoglobin, 13 Gm.). Another patient (C. M., a woman aged 34 years) came under observation because of uterine myomas and was found to have a slightly enlarged spleen but scarcely any leukocytosis (11,000 cells, of which 76 per cent were polymorphonuclear neutrophils). It was 3 years before the spleen was

greatly enlarged. The leukocyte count had increased to only 40,000 (15 per cent myeloblasts, 18 per cent myelocytes and 91 per cent total myeloid leukocytes, with no anemia).

In these 5 cases in which chronic myelogenous leukemia was discovered at a presumably very early stage, it is noteworthy that unexplained leukocytosis (11,000 to 77,000 cells) was the first sign of the disease. In 2 cases physical examination revealed no abnormality. Another patient, whose leukocyte count was as high as 77,000, had slight anemia, and only a few glands were palpable in the angles of the mandible on careful examination. This was the only instance among the 5 cases in which anemia attributable to the leukemic process was found. In the cases in which the leukocyte counts were low, myelocytes, which are so characteristic of the blood picture in the fully developed stage of this disease, were absent or few, and the leukocytosis was chiefly due to an increase in the number of segmented forms.

It is difficult to estimate how long a time would have elapsed before these patients would have sought medical aid on account of symptoms attributable to leukemia. One of these patients was lost sight of after the initial examination, at which a leukocyte count of 77,000 was found. He returned of his own accord because of weakness, 25 years later. A reasonable estimate of the time elapsing from the onset of chronic myelogenous leukemia until symptoms of the disease commonly cause the patient to seek medical attention is probably 2 to 5 years or longer.

Chronic Lymphogenous Leukemia—Data concerning the early phase of chronic lymphogenous leukemia were available in 16 cases. This disease was first discovered in 3 patients when they presented themselves because of symptoms due to prostatic hypertrophy. These men were 59, 67 and 72 years of age, respectively. In H. V. (chart 2) the only finding suggesting disease other than prostatic hypertrophy was enlargement of the tonsils and of a few lymph nodes in the axillae. Neither the spleen nor the liver was enlarged, there was no anemia and the leukocyte count was 8,500. After prostatectomy, glandular enlargement developed slowly, and after 15 years the leukocyte count was 29,000, with 83 per cent lymphocytes. It was 23 years before the liver became palpable, and not until more than 3 years after glandular enlargement was first discovered was there the clinical picture usually associated with lymphogenous leukemia (great enlargement of the lymph nodes and tonsils, 204,000 leukocytes, 3,140,000 red blood cells and a hemoglobin value of 10.1 Gm.). Treatment was instituted shortly afterward, but the patient died 3 months later of bronchopneumonia.

The history of W. A. G. differed from the foregoing in that the first evidence of lymphogenous leukemia was leukocytosis (52,500 cells,

with 97 per cent lymphocytes) with moderate anemia (red blood cells, 3,600,000, hemoglobin, 10.1 Gm) rather than glandular enlargement. This patient died 4.5 years later of pneumonia. In the third case (F. S.) slight glandular enlargement, splenomegaly and moderate leukocytosis (37,300 cells, with 88 per cent lymphocytes) without anemia were the initial findings.

Routine examination, undertaken because sugar had been found in the urine, revealed slight cervical and inguinal glandular enlargement, leukocytosis (34,000 cells, with 86 per cent lymphocytes) and no anemia in a man of 63 years (A. E. S.). This patient died 5 years later. A psychoneurotic disorder brought E. S. (a woman aged 61 years) under observation. Enlargement of the tonsils, a palpable liver and spleen, and leukocytosis (61,400 cells, with 82 per cent lymphocytes) without anemia were the findings of interest. R. P. E., a man aged 73 years, was seen because of "indigestion." There was slight glandular, splenic and hepatic enlargement, the leukocytes numbered 16,800, with 60 per cent lymphocytes, and there was no anemia. He died 2 years later of bronchopneumonia.

Unlike the cases of myelogenous leukemia, the finding of unexplained leukocytosis was the first evidence of the disease in only about a third of the cases of early lymphogenous leukemia. In another third of the cases, glandular enlargement was the sign which first attracted attention. Four patients observed this themselves. By the time they were examined the leukocyte count in 3 instances was still relatively low (19,900, 20,000 and 32,600, respectively, with 73 to 90 per cent lymphocytes). In only 1 case (M. S.) was splenic enlargement the most prominent early sign. The spleen was so large and the blood findings were so normal (leukocytes, 9,000, with lymphocytes, 29 per cent) that splenectomy was performed, the impression being that this was an example of Banti's disease. Subsequently the leukocyte count gradually rose, and when the patient was first seen by one of us, 2 years later, the leukocyte count was 121,000, the lymphocytes numbered 76 per cent and slight glandular enlargement and marked enlargement of the liver were noted. There was no anemia.

It is noteworthy that lymphocytosis was present in a number of cases even when the leukocyte count was still relatively low. Thus in 2 cases in which the leukocyte count was 13,000 and 16,800, respectively, 60 per cent of these cells were lymphocytes; in 2 cases, in which the leukocytes numbered 28,000 and 29,000, respectively, the proportion of lymphocytes was 74 and 83 per cent, respectively; in 3 cases, in which the leukocytes numbered 32,600, 34,000 and 37,000, respectively, the percentage of lymphocytes was 90, 86 and 88, respectively. The early rise

in the proportion of lymphocytes was first noted by Ortner,⁷ and its diagnostic significance was emphasized by Pinkus,⁸ by whose name this sign is sometimes known

Comment—Whereas anemia was not found in the cases of myelogenous leukemia in the very early stages, in several of the cases of lymphogenous leukemia slight anemia was present at what otherwise appeared to be an early stage of the disease

The time interval between the finding of signs which aroused suspicion of the presence of lymphogenous leukemia and the development of symptoms of the disease, as judged by the records in our cases, was about 15 to 25 years. The earlier recognition of lymphogenous leukemia, as compared with that of myelogenous leukemia, in our series is explained by the greater frequency with which glandular enlargement sufficient to attract attention occurred in the patients with lymphogenous leukemia

THERAPEUTIC RESULTS

The results of treatment in cases in which there are adequate data are summarized in table 1. These data are limited to the effects of the first course of treatment, because in patients subjected to many courses of treatment, it is known that sooner or later the response becomes less satisfactory. In the table no distinction is made between the effects of radium and of roentgen rays. Solution of potassium arsenite U S P (Fowler's solution) was given in the manner recommended by Forkner.⁹ All but 1 of the patients with myelogenous leukemia who were given this solution subsequently received irradiation, this is also true of 2 of the 5 patients with lymphogenous leukemia given this solution. Table 1 therefore gives the results of treatment in a total of 30 cases of myelogenous leukemia and 25 cases of lymphogenous leukemia.

Potassium arsenite proved to be of no value in a small group of cases of lymphogenous leukemia, and in the cases of myelogenous leukemia the results of treatment with this drug were less satisfactory than those following irradiation. We have found toxic symptoms following the use of potassium arsenite more troublesome than those associated with irradiation, and the effect on the blood has been more temporary than that produced by roentgen irradiation.

The response to irradiation was slightly better in the cases of myelogenous leukemia than in the cases of lymphogenous leukemia. In

7 Ortner, N. Leukämie und Pseudoleukämie, *Wien klin Wchnschr* **3** 677, 1890

8 Pinkus, F. Die lymphatische Leukämie, in Nothnagel, H. *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1897, p. 90

9 Forkner, C. E. The Administration of Solution of Potassium Arsenite in the Treatment of Chronic Myelogenous Leukemia, *M. Clin. North America* **15**: 1057, 1932

the tabulated data this is indicated chiefly by the greater frequency with which anemia decreased under treatment in the former group of patients than in the latter

TABLE 1—*Results of First Courses of Treatment in Thirty Cases of Chronic Myelogenous Leukemia and Twenty-Five Cases of Chronic Lymphogenous Leukemia*

	Myelogenous		Lymphogenous	
	Irradiation	Solution of Potassium Arsenite U S P	Irradiation	Solution of Potassium Arsenite U S P
Total number of cases	29	8	22	5
Leukocytes				
Decreased	29	6	19	0
Unchanged	0	1	3*	4
Increased	0	1†	0	1
Anemia				
Decreased	13	0	2	0
Unchanged	8	6	17	2
Increased	4	2	1	3
No data	4	0	2	0
Clinical status (objective)				
Improved	27	1	20	0
Unchanged	2†	5	2	3
Worse	0	2	0	2
Clinical status (subjective)				
Improved	28	1	19	0
Unchanged	1	5	3	3
Worse	0	2	0	2

* In 1 of these cases treatment was probably inadequate. In the 2 other cases the leukocyte count was normal when treatment was commenced, in neither case did the red blood cell count rise after roentgen treatment, but the clinical status improved.

† Possibly due to inadequate dosage.

‡ In 1 of these cases the unchanged objective clinical status might have been due to insufficient treatment.

TABLE 2—*Data on Time Intervals*

	Chronic Myelogenous Leukemia		Chronic Lymphogenous Leukemia	
	Time, Years	No of Cases	Time, Years	No of Cases
Time elapsing between onset of symptoms and recognition of disease	1.11	36	1.26	35
Length of life after diagnosis was made	1.68	23	1.07	23
Total time from recognition of disease to death	2.79		2.33	

These results are essentially in agreement with those recorded in the literature.¹⁰

10 (a) Forkner, C. E. *Leukemia and Allied Disorders*, New York, The Macmillan Company, 1938, p. 52. (b) Minot, Buckman and Isaacs.¹ Hoffman and Craver.³ Minot and Isaacs.⁵ Rosenthal and Harris.⁶

DURATION OF LIFE

The average time elapsing between the onset of symptoms and the recognition of leukemia in all our cases, including the cases in which the patients were seen very early in the course, is shown in table 2. The time interval is somewhat shorter than that (14 years) recorded by Minot and his co-workers¹¹. The length of life after the diagnosis was made and the time elapsing between the onset of symptoms and death were shorter than other investigators have found them to be. The average duration of life in the 236 cases of chronic myelogenous leukemia reported by Minot, Buckman and Isaacs,¹ Hoffman and Craver³ and Leavell² was 3.34 years, and the duration in 129 cases of chronic lymphogenous leukemia reported by Minot and Isaacs⁵ and Leavell² was 3.52 years.

There is great variation in the duration of life in cases of chronic leukemia. The natural course of the disease may be extremely slow. A case of lymphogenous leukemia of 25 years' duration was recently described.¹² As many as 14 per cent of the patients treated by Minot and Isaacs⁵ lived 6 to 8 years. Of their patients with myelogenous leukemia,¹ 12 per cent lived 5 to 10 years. Four of the patients with myelogenous leukemia reported by Hoffman and Craver³ lived 16.5, 16, 12.5 and 11 years, respectively. The duration of the disease in these cases must actually have been longer, because in most instances the data referred to duration from the time of the onset of symptoms.

In other cases the disease progresses rapidly, some conditions being encountered in which it is difficult to classify the process as belonging in either of the artificial categories of acute and chronic which custom has set up. In addition, intercurrent infection, cardiac failure or some other disorder not infrequently terminates the course in cases of otherwise slowly progressive leukemia.

INCIDENCE OF INFECTIONS IN CHRONIC MYELOGENOUS AND LYMPHOGENOUS LEUKEMIA, EFFECTS ON LEUKOCYTE COUNT AND CLINICAL STATUS

It is frequently stated that patients presenting the classic clinical and hematologic picture of leukemia often exhibit in the presence of infection a marked decrease in the leukocyte count, even the organs enlarged by the leukemic disorder may decrease in size. This statement has been repeated in textbooks and is found in Forkner's^{10a} recent monograph as well as in Downey's handbook.¹³ It arises from observa-

11 Minot, Buckman and Isaacs¹. Minot and Isaacs⁵.

12 McGavran, C. W. Lymphatic Leukemia of Twenty-Five Years' Duration, *Ann Int Med* **12** 396, 1938.

13 Richter, M. N. Leucemia, in Downey, H. Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2992.

tions made toward the end of the last century Dock¹⁴ reviewed the evidence in 1904 and cited several cases of his own

If this paradox is correct, it is truly a remarkable phenomenon and is of great interest in view of the conception that leukemia is related to malignant tumors. All our cases have been carefully reviewed with the object of noting the incidence of infections and the reaction accompanying these infections. The data are recorded in tables 3 to 5. In tables 4 and 5 the leukocyte counts found at about the time of the highest elevation of temperature are given. Except for syphilis, dental caries and asymptomatic infections like those indicated by chronically infected tonsils, all types of infection encountered in our cases are included.

It is of interest that, although the series consists of 39 cases of myelogenous and 47 of lymphogenous leukemia, there were only 11

TABLE 3—*Pyogenic and Tuberculous Infections in Cases of Chronic Leukemia**

	Myelogenous	Lymphogenous
Acute tonsillitis or peritonsillar abscess	2	0
Otitis media, abscess of brain and acute meningitis	0	1
Chronic sinusitis	0	1
Furunculosis	0	2
Influenza	0	3
Lobar pneumonia (pneumococcus)	0	7
Bronchopneumonia	2	4
Chronic bronchitis	1	0
Bronchiectasis	0	2
Acute infections involving the genitourinary tract	2	4
Subacute or chronic infections involving the genitourinary tract	2	2
Gonorrheal arthritis and bacteremia	1	0
Acute enteritis (Flexner's bacillus)	0	1
Peritonitis (pneumococcus)	0	1
Perirectal abscess	1	0
Acute mastitis and septicemia (beta hemolytic streptococcus) with widespread extrapulmonary tuberculosis	1	0
Total number of infections	12	28

* There were 11 cases of myelogenous and 18 of lymphogenous leukemia.

cases of infection (28.2 per cent) in the former group, whereas 18 (38.2 per cent) occurred in the latter. It was common, moreover, to find more than one type of infection in the cases of lymphogenous leukemia (table 3). The higher incidence of infection in the cases of lymphogenous leukemia is also indicated by a review of the autopsy records. In 28 (14 of each type) of our series of 86 cases an examination was made in the department of pathology. Anatomic evidence of pyogenic infection was found in 5 cases of chronic myelogenous leukemia and in 10 cases of the lymphogenous type.

A striking difference in the two groups was the occurrence of 7 instances of lobar pneumonia in the cases of lymphogenous leukemia and the absence of this type of infection in the cases of myelogenous

14 Dock, G. The Influence of Complicating Diseases upon Leukaemia, *Am J M Sc* 127:563, 1904.

leukemia With 1 exception the outcome was fatal This patient was the only one not observed during the course of the infection at this hospital, but the diagnosis was corroborated by a report from the hospital where he remained during the attack of pneumonia

Clinical improvement in the leukemic signs or a quantitative or qualitative change in the blood in the direction of normal was observed in only 1 case of early chronic lymphogenous leukemia (A E S) This patient's leukemia was accidentally discovered in a routine exam-

TABLE 4—*Leukocytic Picture During Infections in Cases of Chronic Myelogenous Leukemia*

Patient	Infection	Maxi- mum Tem- per- ature, F	Leuko- cytes, Total Count	Differential Counts, %								End Result
				Myeloblasts	Myelocytes	Juvenile Neutrophils	Segmented Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes	
A K	Acute tonsillitis	101.8	90,000	1	42	30	25	0.4	0.3	10	0.3	Recovered
E P	Acute peritonsillar abscess	100.8	241,600	1	14	16	66	1.0	0	2.0	0	Recovered
J S H	Bronchopneumonia	103.6	490,000	13	62	0	23	0	0	0	0	Died
S S	Bronchopneumonia	104.4	5,500*	0	7	0	87	0	1.0	0	5.0	Died†
A G	Chronic bronchitis	101.0	80,000	10	37		46	7.0	0	0	0	Unchanged
H V K	Pyelonephritis	105.4	82,000	6	37	30	26	0	0	1.0	0	Died‡
R B	Chronic cystitis, prostatitis and urethritis	99.4	34,000	6	58	18	8	0	0	0	0	Died‡
C W	Gonococcal arthritis and septicemia	104.4	156,000	2	19	2	70	0	0	4.0	1.0	Recovered
W H R	Gonococcal urethritis (subacute)	100.2	48,700*	0	4	25	65	1.0	3.0	1.0	1.0	Recovered
A G	Acute mastitis and septicemia (beta hemolytic streptococcus) and extra pulmonary tuberculosis	103.0	327,000	0	22	16	53	5.0	2.0	2.0	0	Died†
M N	Perirectal abscess (Bacillus coli)	104.0	21,000*	0.5	9	20	62	0	1.0	7.5	0	Recovered

* In this case the low leukocyte count was the result of roentgen treatment

† In this case the diagnosis was confirmed by autopsy

‡ Death was not due to the infection

ination There was no anemia, but moderate general glandular enlargement as well as leukocytosis (34,000 cells, with 94 per cent lymphocytes) was found The development of an infection of the respiratory tract was accompanied by a slight decrease in the total leukocyte count (to 23,400) on the day when the fever was most marked (102.6 F) At the same time the proportion of lymphocytes decreased to 59 per cent, the absolute number of polymorphonuclear leukocytes thus having increased from about 2,000 to a maximum of 9,600 per cubic millimeter Two weeks later, when the fever had subsided, the leukocyte count was 32,000, with 69 per cent lymphocytes A moderate increase in the size of the lymph nodes occurred during the infection of the respiratory tract

In the majority of the cases the blood picture remained essentially unchanged when infection developed. In 4 cases of lymphogenous leukemia (table 5, C G, R K, C F and I M) an increase in the number of leukocytes actually occurred.

On entry because of prostatic disease, the leukocyte count of C G was 14,920 per cubic millimeter, with 45 per cent lymphocytes. Extrav-

TABLE 5—*Leukocytic Picture During Infections in Cases of Chronic Lymphogenous Leukemia*

Patient	Infection	Maxi- mum Tem- pera- ture, F	Leuko- cytes, Total Count	Differential Counts, %					End Result
				Juvenile Neutrophils	Segmented Neutrophils	Eosinophils	Lymphocytes	Monocytes	
R K	Otitis media, abscess of the brain, acute meningitis	103.0	27,400	0	8	0	91	1	Died*
M B	Chronic purulent pansinusitis, bronchiectasis	101.0	51,200	0	10	0	90	0	Unchanged
J K	Influenza	102.8	57,600	0	4	0.5	95	0.5	Recovered
J W S	Influenza	103.6	84,000						Recovered
A E S	Influenza	102.6	23,400	0	41	0	59	0	Recovered
C G	Urinary extravasation abscess in space of Retzius lobar pneumonia	103.0	41,600	0	21	0	79	0	Died*
		104.6	16,750	0	67	1.0	32	0	
K R	Lobar pneumonia	103.4	122,500	0	30	0	69	1.0	Died*
M C	Lobar pneumonia, acute meningitis septicemia	104.8	72,000	1	1	0	98	0	Died*
M R	Lobar pneumonia, peritonitis	101.8	19,300†	0	45	1	54	0	Died*
C F	Lobar pneumonia chronic cystitis (B coli)	104.0	204,800	0	5	0	95	0	Died*
W W	Lobar pneumonia	103.9	5,200	0	62	0	36	0	Died*
E J L	Lobar pneumonia cystitis (B coli), acute pyelitis		95,000	0	15	0	85	0	Recovered
		103.6	45,000	2	29	0.5	68.5	0	Unchanged
L B	Bronchopneumonia	102.8	30,000	0	5	0	93	2	Died*
R P E	Bronchopneumonia	104.0	26,600	0	51	0	48	1	Died
H V	Bronchopneumonia	103.0	110,000	0	2	0	98	0	Died
I M	Bronchopneumonia, acute cystitis	105.0	120,000	0	0.5	0	99.5	0	Died*
F S	Acute epididymitis	104.0	68,400	6	24	1	66	3	Recovered
R. L	Acute enteritis	103.0	71,000	0	1	0	99	0	Died*

* In this case the diagnosis was confirmed by autopsy.

† In this case the low leukocyte count was the result of roentgen treatment.

asation of urine and the development of an abscess in the space of Retzius was accompanied by fever (102 to 104.6 F) and an increase in the number of leukocytes to a maximum of 65,300 (77 per cent lymphocytes) on the fifth day of fever. On subsidence of temperature to a level of 102 to 100 F following suprapubic cystotomy and drainage of the lateral and prevesical spaces, the leukocyte count gradually dropped to 20,000 (48 per cent lymphocytes). A month after the operation and 12 days after these blood findings were noted, the temperature increased to 104.6 F, and the leukocyte count was found to

be 16,750, with 32 per cent lymphocytes. This, it will be noted, was similar to the blood picture on entry. The patient died the next day, and at autopsy lobar pneumonia, abscesses in the prostate and right testicle, and the typical changes of chronic lymphogenous leukemia were present.

The leukocyte count of R. K. was 17,440 per cubic millimeter, with 60 per cent lymphocytes, on entry. Transfusion was followed by a decrease to 8,500, with 70 per cent lymphocytes. With the development of otitis media the number of white blood corpuscles increased to 27,400, of which 91 per cent were lymphocytes, in spite of irradiation of the glands of the neck and axillas, the count increased to 56,650, with 90 per cent lymphocytes. The number of leukocytes fluctuated between this level and 28,250 until death occurred, 2 weeks after infection set in. In patient C. F. the development of lobar pneumonia was accompanied by an increase in the number of leukocytes from 103,250, with 97 per cent lymphocytes, to 204,800, with 95 per cent lymphocytes. In patient I. M. the development of bronchopneumonia was associated with fluctuation in the leukocyte count between a minimum of 96,000 and a maximum of 200,000.

It is noteworthy that in patient C. G. the increase in the number of lymphocytes, when an abscess developed in the space of Retzius, was accompanied by an increase in the absolute number of myeloid leukocytes from 8,100 to 15,020 per cubic millimeter. The subsequent attack of lobar pneumonia in this case was accompanied by a rise from 9,800 to only 11,390 leukocytes, even though at this time the ratio of the various types of leukocytes was more normal than it had been previously. In patient C. F. the absolute increase in the number of myeloid leukocytes when pneumonia developed was from a level of about 3,100 to 10,240. In patients R. K. and I. M. the absolute number of polymorphonuclear leukocytes changed very little or actually decreased when infection developed.

Our own experience, then, is not in agreement with the statement which has been repeated so frequently in the medical literature. It is curious that there seems to have been no thought of questioning the view that it is common for a remission to occur in cases of leukemia when an intercurrent infection arises. Actually, Dock's¹⁴ study is not beyond criticism. His first patient, who returned for observation 34 days after the diagnosis of chronic myelogenous leukemia was originally made, stated that 2 weeks before she had had influenza. The leukocyte count, which had been 367,070, was 7,500. However, in citing this case it seems to have been overlooked that this patient had been taking potassium arsenite since the diagnosis of leukemia was first made and that she had taken a large amount is indicated by the fact that she com-

plained of numbness and of pruritus. Dock's second patient was also treated with this drug. This patient disappeared from observation, and the evidence offered regarding the influence of infection consists in the finding at autopsy, 1 year later, of severe tuberculosis of the serous membranes and no leukemic changes in the tissues except in the bone marrow. It is stated that there was no leukocytosis at this time, but apparently no leukocyte count was made before death. In Dock's third case, no decrease in the leukocyte count occurred.

Dock cited 6 cases recorded in the literature in which a marked decrease in the leukocyte count occurred in association with acute tuberculosis and 11 other cases in which such a decrease took place in association with other infections. We have been able to examine the original reports of all but 5 of these cases. In 3 cases adequate leukocyte counts were not made, 2 were cases of atypical leukemia and 2 were cases of acute leukemia which may have passed into an "aleukemic" phase. In most of the reports the treatment was not mentioned, but, as Dock himself pointed out, many of the patients whose cases he cited were taking arsenic, sometimes in large doses. Dock's view that the changes in the leukocyte count could not be ascribed wholly or in part to the drug remains a matter of opinion. It is now well recognized that a remission will occur in chronic myelogenous leukemia if large enough doses of potassium arsenite are given.

In 1903 Neutra¹⁵ described a case of chronic lymphogenous leukemia in which the development of lobar pneumonia was accompanied by a striking decrease in the leukocyte count and a diminution in the size of the spleen. He accepted reports of 19 cases recorded in the literature as representing remission in leukemic signs as the result of intercurrent infection but failed to consider the possible effects of arsenical therapy. In the same year Hart¹⁶ recorded a case of chronic lymphogenous leukemia in which the leukocyte count decreased from 1,168,000 to 540,000 when pneumonia developed. Kormoczi¹⁷ described a decrease from 80,000 to 30,000 leukocytes per cubic millimeter accompanying erysipelas in a case of lymphogenous leukemia. Macfie¹⁸ noted a temporary decrease in the leukocyte count in a case of chronic lymphogenous leukemia and in 1 case of the myelogenous type during malarial

15 Neutra, W. Ueber den Einfluss akuter Infektionskrankheiten auf die Leukämie, *Ztschr f Heilk* **24**:349, 1903.

16 Hart, S. Chronic Lymphatic Leukemia Complicated by Pneumonia, *New York M J* **78**:224, 1903.

17 Kormoczi, E. Ein Fall der lymphatischen Leukämie günstig beeinflusst durch Erysipel, *Folia haemat* **11** 297, 1911.

18 Macfie, J. W. S. An Observation on the Effect of Malaria in Leukaemia, *Ann Trop Med* **13** 347, 1920.

infection, and Gamble,¹⁹ who attempted to treat patients with leukemia by the inoculation of malaria, observed a prompt fall in the leukocyte count to less than half the previous count in 2 cases, 1 of each type. After the termination of the paroxysms with quinine, the white blood cell count rose, in 6 and 3 days, respectively, to approximately the previous level.

Few reports on this subject have appeared in recent years. In the case reported by Hickling and Sutliff,²⁰ lobar pneumonia was accompanied by an increase in the leukocyte count from a level of 40,000, with 60 per cent lymphocytes, to 94,000 on the eighth day of the disease. The increase in the total leukocyte count was due chiefly to an increase in lymphocytes, but an absolute increase in polymorphonuclear leukocytes, from 15,000 to 25,000, also occurred. The case reported by MacMahon and Parker,²¹ in which a decrease in the leukocyte count occurred in association with septicemia, cannot be regarded as a case of typical chronic leukemia. Veyssi²² gave a brief account of a case of chronic myelogenous leukemia in which a temporary remission occurred during an acute suppurative process. In the cases of myelogenous leukemia reported by Jaffé²³ and by Gosau,²⁴ roentgen irradiation may have been responsible for the fall in the leukocyte count. In the case reported by Ryan and Medlar,²⁵ no marked effect on the leukocyte count was noted.

A critical review indicates, then, that there is little evidence even in the literature to support the thesis that a remission of the leukemic signs frequently occurs in association with an intercurrent infection. In personal communications, two competent observers have informed us that they recall having seen patients with leukemia in whom a temporary remission occurred during the course of an infection, but several other hematologists of considerable experience have not observed such cases. The occurrence of a remission in association with infection in chronic leukemia, particularly in the lymphogenous type, cannot be denied.

19 Gamble, C. J. Failure of Therapeutic Malaria in the Treatment of Leukemia, *J. A. M. A.* **88** 87 (Jan 8) 1927.

20 Hickling, R. A., and Sutliff, W. D. Pneumonia in a Case of Chronic Lymphatic Leukemia, *Am. J. M. Sc.* **175** 224, 1928.

21 MacMahon, H. E., and Parker, F., Jr. A Case of Lymphoblastoma, Hodgkin's Disease and Tuberculosis, *Am. J. Path.* **6** 367, 1930.

22 Veyssi. Sur un cas de leucémie myéloïde passagèrement améliorée par une infection intercurrente, *Soc. de méd. mil. franç.*, *Bull. mens.* **28** 187, 1934, abstracted, *Am. J. Cancer* **26** 876, 1936.

23 Jaffé, R. H. Tuberculosis and Leukaemia, *Am. Rev. Tuberc.* **27** 32, 1933.

24 Gosau, J. Chronische myeloische Leukämie mit Sepsis tuberculosa acutissima, *Folia haemat.* **52** 271, 1934.

25 Ryan, W. J., and Medlar, E. M. Coexistence of Lymphocytic Leukemia and Far-Advanced Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **36** 212, 1937.

However, a remission is probably a very unusual event rather than a common one. It is noteworthy that ours seems to be the first series of consecutive cases which have been analyzed in regard to the effect of infection on the leukemic picture. The reports in the literature deal with only 1 or 2 cases each and probably have given an erroneous impression of the frequency of remissions caused by infections.

It is of interest that in several of our cases of lymphogenous leukemia, the development of infection was accompanied by an increase, rather than a decrease, in lymphocytes and that in a few instances an absolute increase in granulocytes occurred as well. As already mentioned, Hickling and Sutliff²⁶ noted a similar change. In their case protective antibodies developed in the blood in moderate amount, but no agglutinins were found.

The significance of the increase in the number of lymphocytes is a matter for speculation. The increase in the number of granulocytes probably depends on the persistence of sufficient myeloid tissue to produce mature granulocytes, as Jaffé²⁶ concluded from his study of the inflammatory defense reactions in 10 cases of leukemia. He was unable to confirm the statements of Bickhardt²⁷ and others that leukemic cells may take the place of mature granulocytes, he found that in the absence of myeloid tissue the changes in the tissues in response to infection were similar to those seen in granulocytopenia and in aplastic anemia. If this view is correct, it is easy to see why patients with lymphogenous leukemia are particularly vulnerable to infection, as our data suggest.

SUMMARY

A study has been made of 86 patients with chronic leukemia (39 of myelogenous and 47 of lymphogenous leukemia) treated at the Johns Hopkins Hospital.

Males predominated in both groups, 61.5 per cent of the patients with myelogenous leukemia and 83 per cent of the patients with lymphogenous leukemia being males.

In 72 per cent of the cases of myelogenous leukemia the age at onset was 30 to 59 years, while in 61.7 per cent of the cases of lymphogenous leukemia, symptoms began between 50 and 69 years.

The early phase of chronic leukemia, as determined by the histories of 5 patients with myelogenous leukemia and 16 with lymphogenous leukemia, is described.

26 Jaffé, R. H. Morphology of the Inflammatory Defense Reactions in Leukemia, *Arch. Path.* **14**:177 (Aug.) 1932.

27 Bickhardt, K. Ueber morphologische Befunde bei Entzündungsvorgängen in Fällen von Leukämie, *Folia haemat.* **32**: 83, 1925.

These observations indicate that unexplained leukocytosis may be the first and even the only sign of chronic myelogenous leukemia. In these cases mature cells of the myeloid series rather than myelocytes made up the majority of the leukocytes.

In chronic lymphogenous leukemia, unexplained leukocytosis was the initial sign in only about a third of the cases. Slight glandular enlargement was a frequent early sign. In 1 case splenomegaly was so pronounced and other signs were so minimal that an erroneous diagnosis of Banti's syndrome had been made.

Distinct lymphocytosis was found in a number of cases of early lymphogenous leukemia even when the leukocyte count was relatively low.

Slight anemia was found more often in the early stages of lymphogenous leukemia than in those of myelogenous leukemia.

It is estimated that the time elapsing from the onset of chronic myelogenous leukemia until symptoms of the disease commonly cause the patient to seek medical attention is about 2 to 5 years, whereas this period in cases of lymphogenous leukemia may be only about 1.5 to 2.5 years.

Treatment with solution of potassium arsenite (U. S. P.) was found to be of no value in lymphogenous leukemia and of less value than irradiation in myelogenous leukemia. The response to irradiation was slightly better in myelogenous leukemia.

Statistics concerning the duration of life in cases of chronic leukemia are recorded. It is pointed out that extreme variation occurs in the natural course of the disease in different cases.

Infections were more common in cases of lymphogenous leukemia than in those of myelogenous leukemia.

Contrary to the opinion frequently expressed, infections in the great majority of the cases did not produce a remission in the physical signs or in the blood picture. In only 1 instance did a slight change of this nature occur, and in 4 cases there was an actual increase in the leukocyte count in association with infection.

TRAUMATIC RUPTURE OF THE PERICARDIUM

STUDY OF TWENTY-TWO CASES, WITH TWO AND ONE-HALF
YEAR PERIOD OF SURVIVAL IN ONE CASE,
REVIEW OF LITERATURE

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The literature on traumatic rupture of the pericardium appears never to have been fully assembled and summarized. As recently as 1928, Spitzmuller¹ made mention of only 3 cases in addition to his own. One might infer therefore that this type of injury is a rarity. However, that such an inference is not correct is readily shown by the fact that in 4,107 necropsies performed by the members of the staff of the department of pathology of the University of Oregon Medical School Hospitals and for the coroner of Multnomah County, Ore., over the eight year period between 1929 and 1937, 22 instances of this nature were encountered, none of which had been previously recorded. In all probability other autopsy statistics, particularly if any considerable number of accidental or violent deaths were investigated, would equal or even exceed this figure. Very probably the paucity of information concerning pericardial rupture is due to the fact that it is so commonly but one of multiple injuries terminating fatally and in itself may or may not contribute to the cause of death.

Our interest in the matter was stimulated by the discovery of an extensive pericardial rent, occurring in the absence of evidence of serious damage to the thoracic or abdominal viscera, in a boy who lived for two and one-half years after an accident with but few symptoms attributable to the lesion present at necropsy. In searching the literature a number of reports were found, some of which appeared to have been overlooked by others. Furthermore, we were struck by the inadequacy of certain of the concepts of the mechanism of production of pericardial rupture. For these reasons and because of the interesting problems of cardiodynamics that may have been present in our case, it appeared that another paper on traumatic defects of the pericardium would be timely.

From the Department of Pathology, the University of Oregon Medical School

1 Spitzmuller, W. Ein seltener Fall von Herzbeutelverletzung, Arch f klin Chir 150 551, 1928

REPORT OF CASES

Only the example mentioned in the preceding paragraph demands detailed consideration, the pertinent data of the others are listed in the accompanying table

J F, a 7 year old boy, entered St Vincent's Hospital on July 27, 1934, for tonsillectomy. On this occasion the physical examination disclosed nothing abnormal in the cardiovascular system. Two weeks later he was again admitted to the hospital, one hour after having been run over by a loaded automobile trailer, one wheel of which passed across the upper part of his chest. His sole complaint was of severe pain over the injured area. He was conscious but evidenced some degree of shock. The past history offered nothing suggestive of cardiac or circulatory incompetence.

The blood pressure at this time was 90 systolic and 60 diastolic, the pulse rate was 105 per minute, the respiratory rate 25 and the temperature 98.6 F. Roentgenograms of the thorax and left shoulder were immediately made and disclosed a fracture at the juncture of the middle and the outer third of the clavicle and bilateral thickening of the hilar shadows, with dense peribronchial extensions into the lower lobe of the left lung, but no fractured ribs. However, on physical examination there was noted a distinct deformity over the left third, fourth and fifth ribs, with over-riding fractures of the costochondral junctions of the third and fourth ribs. The leukocyte count at this time was 22,500 with 9 per cent staff cells among the granulocytes. The urine was normal.

After a few hours the temperature became elevated and fluctuated between 98.4 and 100 F for the next four days, returning to normal on the fifth day, when he was discharged. Clinically, the fever and roentgenographic changes in the thorax were interpreted as due to bronchopneumonia. Tuberculosis was suggested as a possibility but was not considered further. With the return of the temperature to normal, the leukocytosis subsided. During the first two days in the hospital the child complained of pain in the chest, but records made no mention of it afterward. At no time were there symptoms or signs of internal hemorrhage. A second roentgenogram of the chest, made on the day of discharge, was reported by Dr. S. E. Rees as follows: "There was still an area of density opposite the left hilar region, extending to the periphery of the lung. There was considerable increased density in the right hilus, with mottling extending into the pulmonary field." After death and necropsy, critical reexamination of the original roentgenograms failed to show the alterations in the heart and pericardium discovered at autopsy. Comparison of the roentgenograms taken immediately after entry and at the time the boy was allowed to go home revealed no more than possible slight enlargement of the heart, and the value of this finding was questionable, since the tube distances were not recorded and may have been different on the two occasions.

On returning home the boy was kept in bed for a short time, but since he was suffering no greater discomfort than was to be expected with the injuries known to be present, he was soon allowed to be up and about. He rapidly resumed his normal activities and vied at all times with children of his own age. Occasionally thereafter there were bouts of mild pain over the site of the injury, which were attributed, probably correctly, to pressure of the displaced ends of the ribs on the overlying muscles. The thoracic deformity persisted, and the protruding knobs at the site of the healed fractures of the ribs could be palpated. To all appearances the child was both healthy and active. In particular there was no complaint on

his part of any symptoms referable to the heart After death of the boy the parents were closely questioned in this respect They had noted nothing more than some shortness of breath after he had carried seven or eight armfuls of wood up a single flight of stairs This was not of recent origin, was not progressive and seemed to have been concomitant with a rather rapid gain in weight Since the mother was of the attentive type and always took the boy to a physician when any symptom developed, it is fairly certain that dyspnea if it existed at all must have been mild Direct questioning revealed that there had been no pain radiating to the shoulder, arm or neck The pain over the site of injury was not of the type originating from the heart, never being incapacitating, sharp or excruciating The family could not recall any particular attack that clinically might fit the autopsy observations Two weeks before death the child was examined by the same physician who attended him at the time of the accident and who had seen him from time to time in the interim Nothing abnormal was found

On the evening of Dec 4, 1936, the boy retired, seemingly well, but at 4 45 a m he was found in bed in a dying condition There had been no outcry, and there was very little evidence of a struggle Emesis was noted It was thought at first that he had choked on some food

Postmortem Observations—The body was 156 cm in length and had an estimated weight of 120 pounds (54.5 Kg) The habitus suggested juvenile hypopituitarism, the skin was white, clear, soft and hairless, the face had a pudgy appearance, the extremities seemed short in comparison to the length of the torso, the fingers and toes were stubby, the breasts were quite well developed, the genitalia seemed rather small, and there was a definite tendency toward girdle obesity with a feminine form of hips and thighs

No evidence of injury, disease or abnormalities of development was found in the abdominal viscera

After the skin and muscles of the anterior aspect of the thorax had been reflected, healed and overlapping fractures of the third, fourth and fifth left costochondral junctures stood out plainly There had been medial and anterior displacement of the lateral fragments of the third and fourth ribs, which on healing had left behind projecting cartilaginous knobs 2.5 cm in length The fifth rib displayed only a button-like swelling at the point of the old fracture Firm bony union had taken place in each instance The contour of the thorax was not appreciably altered

When the thoracic cavity was opened, the heart was seen to be displaced to the left so greatly that the apex impinged against the left lateral wall of the chest, lifting the left lung upward and posteriorly The right cardiac border was in a line drawn perpendicularly downward from the left sternoclavicular joint We were astonished to find that the pericardium failed to envelop the heart, this organ lay quite bare and yet possessed a smooth, glistening, thin epicardial surface save for a single milk-white plaque in the region of the right atrioventricular groove Furthermore, the heart was not adherent to any of the adjacent structures It was boot-shaped, measuring 10.5 cm in the transverse diameter and 7 cm in the vertical direction Both ventricles appeared to be moderately enlarged, especially the right one, which, along with the right atrium, formed practically all the anterior presenting aspect of the heart The conus arteriosus was bulging and abnormally prominent (fig 1) A slight upward and clockwise rotation of the heart was apparent, thus placing the left ventricle posteriorly The change in position could be accounted for by the displacement of the heart to the left and the enlargement of the right ventricle

The apparently missing pericardium was found to have retracted upward and to the right, where it was seen to form a continuous, rolled or at times pleated band encircling the heart and in continuity with the normally and fully developed anterior mediastinal tissue. The thymus was in its usual position over the upper and anterior surface of the pericardium. The retracted and bandlike pericardium was applied snugly about the great vessels and the base of the heart, its free margins were smooth, glistening, rounded and obviously thicker than elsewhere. Anteriorly the folded membrane produced a deep groove in the main pulmonary artery just distal to its valve and coursed over the right atrioventricular sulcus.



Fig 1—In the upper drawing is shown the anterior view of the thoracic organs and a portion of diaphragm of the 9 year old boy. The heart is displaced to the left, crowding the left lung upward. The lowermost hook pulls on the right border of the pericardium, which is seen passing upward and to the right over the pulmonary artery, greatly compressing the vessel and causing the conus arteriosus to bulge in a startling manner. In the lower drawing the left cardiac border is displayed. Covering the atrioventricular sulcus is the retracted, thickened pericardium, which has almost completely inverted the left atrial appendage

and right atrial appendage without compressing either. To the left of the pulmonary artery the accordion-like band of pericardium narrowed down like a knife blade, first to a width of 2 cm, finally, at the base of the heart posteriorly it existed only

as a low white ridge. The left phrenic nerve could be traced through this ridge of pericardium and into the diaphragm at the usual site, on the right side the same nerve took its normal course. The aorta, left atrioventricular sulcus and pulmonary veins, while closely approximated by the retracted pericardium, gave no indications of undue pressure on them. The superior and inferior venae cavae likewise appeared to have escaped damage. The left atrial appendage, however, was almost completely invaginated into the atrium, but it had not become adherent and was everted easily. In general, it appeared that the pericardium, which was like a purse string, was tight anteriorly and loose over the posterior surface of the heart. It is recognized that this may not have been the situation during life, but if our concept of upward rotation of the apex is correct, it would account for the appearance noted at autopsy. In this connection it should be mentioned that the body had been arterially embalmed for about ten hours prior to the post-mortem examination, allowing time for good hardening of the organs and making it reasonable to assume that the positions noted were not far different from those during life. In spite of the frequent pleating of the retracted pericardial margin, adhesions had not formed, and the whole membrane, which could be unfolded easily and without undue stretching, proved to be of sufficient size to accommodate the entire heart. When the pericardium was thus reapproximated, it appeared that the line of rupture had been along the entire left border, leaving an opening just large enough to permit the extrusion of the heart.

The wall of the obviously dilated right ventricle measured 0.5 cm in thickness. The right chambers were filled with postmortem clots. There were no lesions in the tricuspid or pulmonic valves. The interatrial and interventricular septums were intact. The superior and inferior venae cavae were unchanged. A finger passed into the prominent pulmonary conus and through the valve met with an obstruction at the point where the pericardial band passed over the artery. After thorough fixation, the pulmonary artery and its branches were examined from above after severance of the constricting band of pericardium, all contained postmortem clots. A difference in size was apparent between the right and left branches, the former having a diameter of 2 cm and the latter a diameter of 2.7 cm. Approximately 3 mm distal to the commissures of the cusps of the pulmonary valve, the lumen of the main artery was so constricted that a 4 mm probe was passed with difficulty, here the wall was grooved to a depth of 3 mm and for a width of 2 mm. The lumen at the point of narrowing contained a snugly fitting post-mortem clot 4 mm in diameter. It is reasonable to assume that the size of the clot represented the approximate caliber of the vessel at the time of death. At the point of constriction, the intima was pearly white and lacked the discoloration due to hemolysis seen elsewhere (fig. 2).

The left chambers of the heart proved to be dilated and to contain only post-mortem clots. The wall of the left ventricle had a maximum thickness of 1.4 cm. The trabeculae carneae were flattened. The mitral and aortic valves were normal. When the inverted appendage of the left atrium was pushed out, it immediately resumed its natural position and shape. This feature, along with the lack of thrombus formation or adhesions, strongly suggested that the pericardium had not been in the position in which it was found for any appreciable time prior to death. The ductus arteriosus was obliterated.

The lungs displayed pronounced edema. The larger air passages, including the larynx, were patent. Aside from a mild degree of acute passive hyperemia, the other organs were unchanged.

Microscopic sections of the myocardium displayed only slight hypertrophy, no scarring such as might readily follow the healing of a cardiac contusion was discerned. In the aortic intima were several minute intimal lesions containing lipoid-filled cells.

COMMENT ON AND INTERPRETATION OF THE POSTMORTEM OBSERVATIONS

The clinical and autopsy data offer many points of interest and importance. It was recognized at the outset that the foremost problem was to establish whether the pericardial defect was of congenital or traumatic origin. Important features favoring the latter and against the former type of origin were (1) the well authenticated clinical history and roentgenologic proof of injury of the thorax with frac-

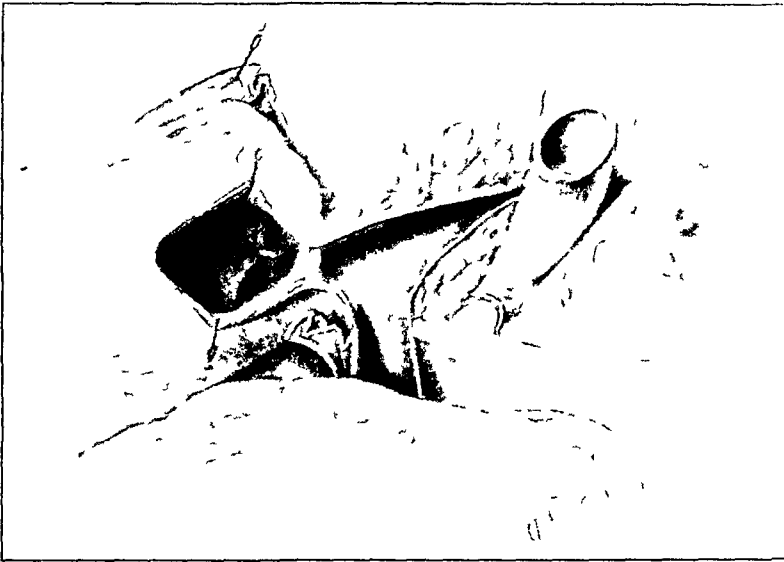


Fig 2—The pulmonary valve, pulmonary artery and its main branches, as viewed from above after having been hardened in solution of formaldehyde and opened. Just without the valve is a deep constriction of the main artery caused by the purse string action of the ruptured, retracted and pleated pericardium, the margins of which may be seen immediately below the vessel and again above, where a hook has been placed. Portions of the lungs and trachea are included in the drawing.

ture of the left clavicle and the third, fourth and fifth ribs, (2) the absence of symptoms or signs of a pathologic cardiac condition either prior to or after the accident, (3) postmortem absence of chronic dilatation of the heart, which is often reported to occur in the presence of congenital pericardial defects, (4) acute rather than chronic passive hyperemia, as would be expected if the heart had long been dilated, (5) a normally developed mediastinum, (6) the normal position and distribution of both phrenic nerves in relation to the pericardium and

diaphragm, and (7) nonadherence of the retracted and pleated pericardium to itself or the surrounding structures and its ample size, (it accommodated the heart when stretched out and reapproximated) Plaut² has emphasized the position of the phrenic nerves as one point in differentiating between congenital and other forms of pericardial defects. In the congenital type the left phrenic nerve is likely to course superficially directly beneath the sternum, while the right nerve lies at a deeper level. The smaller the rudiment of pericardium, the farther to the right is the corresponding phrenic nerve displaced.³

The time at which herniation of the heart or retraction of the pericardium or a combination of the two took place is uncertain. The lack of pain of cardiac origin or of attacks of failure of the right side of the heart at any time after the accident and the easily retractible left atrial appendage favored terminal extrusion. Also, in some of the previously recorded examples of traumatic rupture of the pericardium in which death was not immediate, the pericardium had been bound to surrounding structures by blood clot or fibrous adhesions, nothing of the kind was present in our subject.

While the history suggested the occurrence of mild attacks of pain which could be explained by a temporary and intermittent escape of the heart through the pericardial rent, it is impossible for us to believe that the degree of obstruction of the pulmonary artery so plainly evident at necropsy could have existed for any length of time. Rather, we feel that it was the actual and immediate cause of death and could not have existed constantly during the two and a half years of life after the injury. In support of this concept were the lack of hypertrophy of the right ventricle and the presence of evidence of its acute dilatation and of generalized acute passive hyperemia. The final mechanism must have been akin to that operating in embolic occlusion of the pulmonary artery, save that the obstruction was not complete and was applied from without rather than from within the vessel. In this connection the observations of Fineburg and Wiggers⁴ may be cited. In experimental obstruction of the pulmonary artery it was shown that more than 58 per cent constriction not only resulted in congestion of the right side of the heart and failure but also introduced another factor, namely, a lowered blood supply to the left side of the heart, a drop in systemic blood pressure and ischemia of the coronary arteries, thus causing dilatation and failure of the left side of the heart and an extremely rapid failure of the right side, attributable to a lack of arterial blood supply to the

2 Plaut, M. Ueber zwei weitere Fälle von Defekt des Herzbeutels, Frankfurt Ztschr. f. Path. **12** 141, 1913.

3 Plaut,² p. 146.

4 Fineburg, M. H., and Wiggers, C. J. Compensation and Failure of the Right Ventricle, Am. Heart J. **11** 255, 1936.

myocardium Beck's⁵ triad of clinical signs of compression of the heart itself, namely, (a) a low arterial pressure, (b) a high venous pressure and (c) a small quiet heart, expresses the same thought in different words

ADDITIONAL CASES

We are including references to additional cases largely because of the meager statistics relating to the effects of trauma on the pericardium. While the essential facts concerning these cases are given in the accompanying table, certain features contained therein deserve amplification.

In the majority of the cases the injuries were sustained in motor vehicular accidents, the victim being struck and knocked down or run over on both. One victim was struck almost simultaneously by two cars. Others were thrown from automobiles or pinned beneath them. Four deaths were the result of falling, 1 victim was crushed by an elevator.

The youngest patient, whose case has just been reported in detail, was 9 years of age at the time of death and the eldest 84. The age of the majority fell between 40 and 50, i. e., the years of activity in industry but of decreasing agility.

In 13 the pericardium was ruptured on the left side, mostly along the margo obtusus of the heart, in 4 the rupture was located on the right side, for the most part somewhat anteriorly, 1 patient displayed multiple lacerations, while the site of rupture in 1 case was inadequately described.

The heart was found protruding through the opening in the pericardium 7 times. In 4 cases the descriptions were vague, but from the nature of the lesions it would seem impossible for cardiac herniation to have occurred. One example is particularly interesting because of its similarity to the case just described in detail, for while death was sudden and the result of other extensive injuries, the pericardium nevertheless had slipped backward and was so tightly encircling the midportion of the left ventricle that the muscle at this point was both depressed and blanched. In another case of pericardial rupture, the interatrial septum was torn across, and in another contusion of the myocardium was displayed.

With the 1 exception, none of the victims survived for any appreciable time, all of them dying as a result of multiple injuries almost at once.

As a rule, the side on which the pericardium was torn, whether right or left, corresponded to the side from which the force came. Two cases proved to be exceptions to this rule. In attempting to classify these, however, one familiar with vehicular accidents can readily under-

⁵ Beck, C. S. Two Cardiac Compression Triads, *J. A. M. A.* **104**: 714 (March 2) 1935.

Summary of Data on Twenty-Two Cases of Traumatic Rupture of the Pericardium Encountered in Routine Necropsies

Case No	Age, Years	Cause	Site of Injury of Pericardium	Perforation of Heart	Direction of Force	Accompanying Injuries	Mechanism of Rupture	Comments
1	14	Thrown from car	Left	No	Left	Rupture of lung, liver, spleen and adrenals	Compression	5 cm tear in pericardium
2	21	Elevator	Anterior and right posterior	No	Uncertain	Rupture of lung, liver and inferior vena cava	Compression	Heart herniated
3	?	Street car	Left and inferior	No	Left	Rupture of spleen and left lung	Laceration ?	No herniation of heart
4	55	Fell 2 stories	Left base	Yes	Uncertain	Rupture of lung fat embolism	Laceration	Laceration due to sternal fragments
5	45	Crushed by auto	Left	Yes	Uncertain	Fractured ribs, hemorrhage	Laceration	Heart herniated
6	72	Automobile	Left	Yes	Uncertain	Fracture of spine and sternum rupture of liver	Laceration	Torn inferior vena cava
7	81	Run over by car	Right anterior	Yes	Left	Fracture of spine and ribs	Laceration	Torn inferior vena cava
8	70	Struck by 2 cars	Anterior	Yes	Right	Injury of lungs, liver, diaphragm, spine and ribs	Perforation	Heart herniated ?
9	44	Fall	Right anterior	Rupture	Uncertain	Rupture of diaphragm, right hemothorax	Compression	No ribs fractured
10	56	Run over by car	Anterior	Yes	Left	Rupture of lung, spleen and liver, fracture of ribs	Perforation ?	Heart herniated ?
11	45	Fell 6 stories	Several	Yes	Left	Fracture of sternum, ribs and skull	Laceration	Heart not protruding
12	?	Automobile	Anterior	Rupture	Right	Fracture of right ribs and legs	Compression	No protrusion of heart
13	78	Automobile	Posterior left	No	Left	Fracture of ribs and spine rupture of liver and spleen	Compression	No protrusion of heart 10 cm pericardial tear
14	40	Fell 6 floors	Left	No	Left	Fracture of spine and ribs rupture of left lung, liver and kidney	Compression	Heart herniated 8 cm pericardial tear
15	15	Automobile	Right anterior	No	Right	Rupture of liver, spleen, kidney and diaphragm	Compression	Heart not herniated no fractured ribs
16	42	Automobile	Inadequately described	No	Uncertain	Rupture of liver, lung and left kidney	?	Small pericardial tear
17	19	Automobile	Left, pulmonary vein downward	Yes	Left	Rupture of spleen, fracture of left ribs laceration of left lung	Laceration	Torn pulmonary veins
18	35	Automobile	Left side	No	Right	Rupture of liver, diaphragm and interauricular septum	Compression	Rupture on side opposite applied force
19	45	Fell 3 stories	Left	No	Uncertain	Fracture of ribs and sternum	Compression	Heart herniated
20	65	Automobile	Left	No	Left	Rupture of aorta superficial laceration of vena cava fracture of ribs and sternum	Compression	Heart herniated through tear and strangulated
21	60	Automobile	Left	No	Probably left	Rupture of brain stem liver, kidney and spleen fracture of ribs	Compression	Herniation of heart
22	9	Run over by auto trailer	Left	No	Left	Fracture of left ribs and clavicle	Compression	Herniation of heart strangulation of pulmonary artery

stand the difficulty encountered in determining solely from a written record the exact direction from which multiple forces were applied

In the main it appears that two mechanisms of pericardial rupture exist (1) compression and (2) laceration or puncture by the ends of fractured bones. A combination of the two is likewise possible, the pericardium bursting under the effects of pressure alone and before the ribs give way, but in such cases, particularly when the pleura was torn by the fractured ribs in any situation in which it would be at all possible for spicules of bone to have produced the holes in the pericardium, we have considered it best to regard the lesions as penetrating wounds due to the ends of bones. On the other hand, in certain cases in which the fractured ribs were so located that penetration of the pericardium was impossible, it has seemed logical to classify the condition as a pure compression rupture of the pericardium.

REVIEW OF THE LITERATURE

One of the earliest, certainly the most exhaustive and even today still one of the valuable contributions on the subject of traumatic cardiac and pericardial wounds was published by Fischer,⁶ in 1868. The purpose of Fischer's paper, based on 452 wounds (401 of the heart and 51 involving the pericardium), was to refute the then generally held belief that wounds of the heart and its enveloping membranes were absolutely fatal and, further, to catalog the diagnostic symptoms of such conditions. Personal cases and those he found reported in the literature were grouped according to the etiologic factors, the site and depth of the wounds and the duration of life after injury. We mention the manner of arrangement because it explains the lack of strict chronologic order in the numbering of the case reports of pericardial rupture cited by Fischer, abstracts and excerpts from which are given herewith. The case numbers in parentheses are Fischer's numbers. All instances of perforation of the pericardium by sharp instruments or bullets are intentionally omitted.

CASE 1 (case 374) —(Hewett, P. *London M Gaz* 4 870 [May 14] 1847.) We were fortunate in obtaining the original article, and the abstract is from that source rather than from Fischer's article. Five instances of rupture of the heart and vessels were presented. Of these, only the second was an example of pericardial rupture. A man aged 53 was brought into St George's Hospital dead, the report being that he had been kicked in the chest by a horse with enough force to send him backward several feet. The passersby ran to the man's assistance, but he was dead. At necropsy no marks of violence were observed, but when the skin was removed from the chest, some extravasated blood was found in the soft tissues. In the second piece of the sternum was a transverse fracture, without displacement, despite the laceration of the periosteum on both sides. The left second to sixth

⁶ Fischer, G. Die Wunden des Herzens und des Herzbeutels, *Arch f klin Chir* 9 571, 1868.

ribs were fractured in two places, close to the cartilages and near the spine, on the right side the second to fourth ribs were fractured about 3 inches (7.6 cm) from their cartilages. The pericardium was filled with blood, and an extensive laceration was seen on the left side. Old adhesions between the lung and the pericardium prevented the escape of blood into the pleura. The right ventricle of the heart presented a transversely directed laceration of its anterior surface at the junction with the pulmonary artery, through which the tip of the index finger was easily passed. The lungs were not traumatized, the other viscera were not examined.

CASE 2 (case 375) —(Vater, C. *Ephemer. nat. curios.* Dec. III. ann. IX and X, Nuremberg, Frankfurt and Leipzig, 1706, obs. 164). A 30 year old woman was crushed against a wall by a wagon (1695). There were fractures of the first and second left ribs near the sternum and a fracture of the left clavicle. The pericardium was only slightly injured, but the right ventricle was torn at the top, with much blood in the pericardium. It was clearly stated that the rupture was not produced by the fractures but from compression of the thorax.

CASE 3 (case 376) —(Niemann, A. *Ztschr. f. d. Staatsarznk.*, 1861, p. 326). The victim had been run over. The pericardium had a long tear near the vena cava, and the right ventricle had a tear near the attachment of the vena cava. There was much blood in the mediastinum, and the pericardial sac was distended with blood to four times its natural size.

CASE 4 (case 379) —(Dupuytren, G. *Clin. chu.* 2 215, 1839). A man aged 41 years was pressed against a wall by a wagon tongue, sustaining fractures of several ribs and a diagonal break in the sternum at the junction of both the upper and the lower third. The upper fragment was forced deep into the mediastinum. The man was relatively well until the fourth day after injury, when oppression and a small pulse beat were noted. His condition ranged from suffocation to improvement for ten days. Subcutaneous emphysema was lacking, there was an ecchymosis extending from the chest to the hip. Death due to pericarditis occurred on the twelfth day. It was found that the upper fragment of the sternum had penetrated the pericardium and torn a third of the way through the right ventricle. There was bloody serum in the right pleural cavity, and old strong adhesions were present between the pleurae.

CASE 5 (case 380) —(Elleau, A. H. *Essai sur les ruptures du cœur*, Thesis, Paris, no. 186, 1857, p. 14). A man 20 years of age fell from a tree and died within a few minutes. There was rupture of the pericardium and of the left ventricle.

CASE 6 (case 391) —(Morel-Lavallee, V. A. F. *Gaz. d. hôp.* 1860, p. 19, 1864, pp. 46, 48, 51 and 53). The first case, described in the paper of 1860, concerned a carpenter who fell a distance of 6 meters, striking on his left side. He was rendered unconscious and when seen was in shock. Later he became lucid, but after five hours, during which vomiting took place, he lapsed into unconscious-

7 The original articles were abstracted by us. Evidently the same cases referred to by Fischer were reported in the following articles: Laceration of the Pericardium and Fracture of the Skull, *Bull. Soc. de chir. de Paris* 1 64, 1860; Rupture of the Pericardium. Water-Wheel Murmur, Mill Murmur, *Gaz. med. de Paris* 19 695-729, 771 and 803, 1864.

ness Examination the following day disclosed injury to the head, fracture of the sternoclavicular joint or clavicle and indications of injury over the precordium Lavalée said he heard a loud "double systolic, 'water-wheel,' murmur," the sounds were alternately loud and soft and sharply interrupted, like the impact of water on the blades of an overshot water wheel He concluded that this could have been made only by fluid or air or both which was being drawn in and out of the pericardial sac and that a pleuropericardial communication was necessarily present The man lived for three days Postmortem examination disclosed a fracture of the cartilaginous portion of the third rib, without displacement, and rupture of the pericardium along the left border 3 cm above the apex, the tear had irregular edges, was round and permitted the insertion of the little finger Fluid was present in both pleural and pericardial sacs, thus confirming the observer's contention Specific mention was made that continuity of the parietal pleura beneath the fractured rib persisted Fracture of the skull with subdural hemorrhage was the direct cause of death

Comment—In his discussion the author stressed the value of *Bruit de roue hydraulique* or *bruit de moulin* as a diagnostic sign of pericardial rupture This has not been mentioned by any subsequent writer As to the mechanism of production of rupture of the pericardium, Lavalée said he felt that the lungs and heart were crushed against the vertebrae during the impact and that the tear was produced by shearing or rubbing of the membrane against the bone

This case and 2 others formed the basis of a publication appearing in 1864 Again Lavalée mentioned having heard the "water wheel murmur" One of the new cases appears to us to have been an example of pneumohydropericardium and is not included here The other (Fischer's case 439) was that of a workman who fell three stories onto some prominence and then to the ground, sustaining a compound fracture of the left leg, left hemiplegia and shock Hematuria was noted Icterus appeared shortly, suggesting rupture of the liver Heard most distinctly over the nipple region at each seventh, fifteenth and twentieth pulsation and repeating itself four or five times was a murmur like the sound produced by blowing in an empty bottle It vanished when the patient was upright, reappeared when he was prone and disappeared after five days, when a precordial rub developed The positive diagnosis of a pleuropericardial communication was confirmed at autopsy, nine days after the accident, by the finding of a most remarkable rupture of the pericardium It consisted of five great tears which left webs of pericardium and holes, the largest of which admitted a whole hand It measured 10 by 13 cm Herniation of the heart was noted There were no demonstrable fractures of the ribs, the findings in other parts of the body were insignificant In this paper the author suggested the possibility that rupture had been produced by vibration, although he again said he considered that friction may have been responsible

These 2 cases are most remarkable because the patients were seen by the same physician, who established the correct diagnosis of a rare

lesion during life The second example is noteworthy on account of the extensiveness of the pericardial damage and further because it demonstrates that the pericardium is not an indispensable structure, since the patient survived for a number of days Finally, it was Lavallee who first ventured a plausible explanation of the cause of pericardial rupture

CASE 7 (case 392) —(Loir, J N *Dissertation et propositions sur quelques points d'anatomie de physiologie et de pathologie*, Thesis, Paris, no 45, Paris, Mequignon-Marvis, pere & fils, 1835) A driver 23 years old was caught between the wheels of two wagons, he quickly lost consciousness and died There were fractures in the posterior halves of the eighth and ninth ribs and blood in the left pleura and the pericardium, where a 2 inch (5 cm) opening was seen On the posterior surface of the heart was a 1½ inch (3.8 cm) wound communicating with both chambers The injury had been caused by the sharp fragments of the eighth rib The spleen was ruptured (Fischer stated that this case was cited by Choisy from Bouillaud [Bouillaud, J B *Traite clinique des maladies du coeur*, Paris, J B Bailliere, 1835, vol 2, p 499] and in the works of Dupuytren and Marx [Dupuytren, G *Leçons orales de clinique chirurgicale*, Paris, Germer-Bailliere, 1839, vol 2, p 213])

CASE 8 (case 395) —(Duverney, J G *Traité des maladies des os*, Paris, De Bure l'aîné, 1751, vol 1, p 275) A man fell on a stone while bowling, splintering and crushing the body of the sternum and tearing the pericardium and right auricle

CASE 9 (case 399) —(Wilkin and Lees *Dublin J M Sc* 2 174, 1837) A brewer was run over, he got up and drove on for another hour and then went to the hospital, complaining of pain He died immediately after turning on his side There was a fracture of the fifth rib, the end of which penetrated the pericardium and right auricle, plugging the hole in the former but not in the latter Apparently both were closed at first and became loosened when he was lying down

CASE 10 (case 411) —(Gamble, J S *Researches in Pathological Anatomy and Clinical Surgery*, London, H Bailliere, 1856) A man of 38 fell from a wagon The pericardium was torn anteriorly, a rent the size of a goose quill was seen in the auricle and the liver was torn The heart was otherwise normal

CASE 11 (case 416) —(Dickinson *London M Times*, Jan 31, 1863) A child of 5 years was run over and brought into the hospital dead There were no external injuries, but the pericardium was full of blood, which issued from a tear in the tip of the heart Both ventricles were open, and the heart was considerably torn, as was also the pericardium There were no fractures

CASE 12 (case 417) —(St Thomas' Hospital, London, von Chelius, M J *A System of Surgery*, translated by J F South, Philadelphia, Lea & Blanchard, 1847, vol 1, p 546) A man was run over and then walked about one hundred steps He died in about nine hours of suffocation There were fractures of the first two ribs on the right side and of the upper five ribs on the left side A sharp end had been forced into the pericardium and had injured the heart near the tip Both the pleurae and the pericardium contained blood The right side of the diaphragm and the apex of the left lung were torn

CASE 13 (case 420) —(Mayer *Med-chin Ztg*, Aug 31, 1835) A farmer was thrown from a raft by a falling log without being touched by it. He fell into the water and although brought up immediately proved to be dead. There was 5 pounds (2.3 Kg) of blood in the thorax. A tear was seen in the pericardium near the attachment of the aorta, another occurred at the tip of the heart. The myocardium was healthy.

CASE 14 (case 422) —(Casper, J. L. *Practischer Handbuch der gerichtlichen Medicin*, Berlin, A. Hirschwald, 1857, p. 122) A man aged 24 was hurled with great force from a wagon against a poplar tree. Outward evidence of injury was lacking. The spinous process of the first thoracic vertebra was broken. The heart was completely torn from the vessels and lay free in the thoracic cavity. The pericardium was likewise wholly divided. The heart substance was normal. Three quarts (2,840 cc) of blood occupied the left side of the thoracic cavity. The lungs and liver were torn.

CASE 15 (case 423) —(Casper, J. L. *Klinsche Novellen zur gerichtlichen Medicin*, Berlin, A. Hirschwald, 1863, p. 347) A man was instantly killed by a falling iron beam. The left side of the chest was completely crushed, and there were six or eight tears in the left lung, which were not produced by the fractures. The pericardium was torn its full length, and the heart, separated from its great vessels, lay free in the pericardial sac.

CASE 16 (case 425) —(Flügel *Aerztl. Int.-Bl.*, 1859, no. 26) A boy 17 years of age was caught in a gear and was dead when rescued. A few drops of blood issued from the nose and mouth, there were abrasions on the body. The fourth rib was fractured near the nipple. Both pleural sacs were filled with blood. The pericardium displayed a posterior tear through which the heart herniated. Tears existed in the lungs, liver and spleen.

CASE 17 (case 426) —de Berghes *Wchenschr. f. d. ges. Heilk.*, 1844, no. 20, p. 326) A man was crushed under a falling tree. The thorax and abdomen were split so that a large part of the viscera came out, tearing the heart from its attachment and allowing it to fly for a distance of ten steps from the body. The heart was lacerated in several places superiorly, so that the fingers could be inserted into the ventricles, no traces of vessels or valves remained on the organ. It should be noted that although no mention of the pericardium was made, it must have been ruptured.

CASE 18 (case 430) —(Sanson, A. *Plates du coeur*, Thesis, Paris, no. 259, 1827, obs. 24, p. 34) A man of 40 years was struck over the chest by a wagon tongue, which fractured several ribs and the sternum. He was found in shock and was treated by bandaging and bleeding. Death supervened on the thirteenth day. The fourth to sixth ribs were broken 3 inches (7.6 cm) from the sternum, and in the latter was a transverse fracture. A pint (475 cc) of bloody serum was present in the right pleura. The upper fragment of the sternum was forced inside the pericardium, and in this region there was a nonpenetrating wound, measuring about 1 inch (2.5 cm) in length, directed transversely on the surface of the heart. The pericardium was reddened and had adhesions.

CASE 19 (case 432) —(Watson *New York J. Med.* vol. 3, p. 351) In this case there was a fracture of the sternum which tore the pericardium but compressed the heart only slightly.

CASE 20 (case 435) —(Irving, J Rupture of the Heart from Accident, *Lancet* 1 241, 1859 Fischer listed only the reference, we have made the abstract) A boy of 16 years was run over by an empty wagon, the wheels crossing the chest, death was instantaneous The face and body generally appeared pallid one or two of the spinous processes of the dorsal vertebrae were fractured, the fifth and tenth right ribs were broken The pericardium showed a tear, which barely admitted the forefinger, communicating with the right pleura The heart was the seat of three ruptures, there were three lacerations in the lower lobe of the right lung opposite the fractured ribs Irving said he felt that the first wheel must have come on the heart when the ventricles were full and must have burst them, whereon the pericardium immediately distended and was ruptured by passage of the second wheel

CASE 21 (case 436) —(Christison, cited by Watson *New York J Med* vol 3, p 96) Rupture in this case was due to a fall No details were given

CASE 22 (case 437) —(Christison) In this case rupture was due to a blow, no further information was given

CASE 23 (case 438) —(Costa de Saida *Gaz d hôp* 26 413, 1853) A 45 year old man fell from the fourth floor of a house, sustaining a rupture of the entire left side of the pericardium, extrusion of the heart and three fractures of the sternum, with the first fragment pressing posteriorly, resulting in a tear in the ascending aorta, lung and diaphragm Additional fractures and dislocations were present He died at once

CASE 24 (case 440) —(Lente, F *New York J Med* 17 171, 1851) A man aged 36 was struck by a bale of hay on board a ship and was precipitated 20 feet (6 meters) into the hold The results included a comminuted fracture of the sternum, laceration of the pericardium, contusion of the heart and fracture of a cervical vertebra

CASE 25 (case 441) —(Casper, J L *Practisches Handbuch der gerichtlichen Medicin*, Berlin, A Hirschwald, 1857, p 124) A 44 year old man fell 46 feet (14 meters) into a cellar and probably died at once The pericardium was torn along its entire length, but the heart was not injured The liver and spleen were lacerated, the ribs were "bent in" and the skull was fractured

CASE 26 (case 442) —(Hermann, J *Oester med Wchschr*, 1846, p 347) There was rupture of the pericardium and diaphragm allowing herniation of the small bowel into the thoracic cavity

CASE 27 (case 444) —(Stokes, W *Edinburgh M J*, July 1, 1831, *London M Gaz*, July 30, 1831, p 560) This case was not confirmed by autopsy but is of great interest clinically It is discussed at end of this paper

CASE 28 (case 449) —(Morel-Lavallee, cited by Casper, J L *Practisches Handbuch der gerichtlichen medicin*, Berlin, A Hirschwald, 1857) A patient who had a water wheel murmur recovered, autopsy was not performed We are inclined to feel that this was an example of pneumohydropericardium, although Morel-Lavallee made a clinical diagnosis of rupture of the pericardium

CASE 29 —(This case was not included in Fischer's review It was reported by Duka⁸ in 1862) A man aged 65, a Mohammedan, fell during a scuffle and

8 Duka, T A Case of Rupture of the Right Ventricle of the Heart and Pericardium, *Indian Ann M Sc* 8 257, 1862

suddenly expired. The left pleural cavity and pericardial sac were distended with blood. A few "lines" above the apex of the heart and covered by the lower lobe of the left lung was a small horizontally directed aperture in the pericardium, with seepage of blood into the torn margins of the membrane. The wall of the right ventricle had two rents, one complete and the other only partial. The heart displayed fatty degeneration and extensive atheromatous deposits in the main arteries. Rupture of the pericardium was mentioned as the most remarkable feature of the case, but the reason therefor was not stated.

CASE 30—(Damman,⁹ 1872) In this instance, pericardial rupture was observed at autopsy. The person had fallen out of a *Gietjariaa* (a local type of conveyance in Cape Town, South Africa), and died immediately. In a case in which the patient was observed clinically, Damman suggested the possibility of ruptured pericardium, permission for necropsy was denied, and the diagnosis could not be confirmed.¹⁰

CASE 31—(Joubin,¹¹ 1873) The patient was struck on the chest and died. A rent in the pericardium was found at the postmortem examination.

CASE 32—(Lewtas,¹² 1876) A coolie fell about 40 feet (12 meters) into the hold of a ship, death ensued two hours later. There was extensive subcutaneous emphysema, fractures were found in the left clavicle and in many of the ribs on the left side, producing many wounds in the left lung. In the right side of the pericardium was a 2 inch (5 cm) rent, the edges were discolored with blood which had extravasated into the membrane. Through the opening the heart could be seen in its normal position. Another and smaller rupture of similar appearance was found in the left side of the pericardium close to the apex of the heart. The pericardial sac was devoid of blood, but about 6 ounces (178 cc) that may have come from the torn membrane lay in the right pleural sac. The right ribs and lung, liver and spleen were uninjured. Lewtas had never before encountered a pericardial rupture.

CASE 33—(Allan,¹³ 1878) A man aged 48 was crushed when a bale of cotton struck his back. Considerable hemorrhage from the urethra warranted a clinical diagnosis of fracture of the pubic bone with rupture of the membranous urethra. He had great pain in the cardiac region, incessant painful cough and an anxious expression. Elevation of the temperature and slight pneumonia persisted for a week. The temperature returned to normal and continued thus for fifteen days, followed by signs of pleurisy and pericarditis. Death supervened one month after his admission to the hospital. At necropsy, bilateral serofibrinous pleuritis, pulmonary congestion and edema and a pericardial tear along the whole left border were present. When the anterior part of the left lung was lifted from the peri-

9 Damman. *Verhandel v h Genootsch t Bevoord d Nat Genees- en Heelk te Amsterdam* 3 13, 1872-1873.

10 This case report was translated for us by Dr J G Huizenga, Holland, Mich.

11 Joubin, F. *De la déchirure du poumon sans fracture de côte correspondante, considérée au point de vue de son mécanisme et de ses symptômes*, Thesis, Paris, no 304, 1873, cited by Shackelford, R T. *Hydropneumopericardium*, J A M A 96 187 (Jan 17) 1931.

12 Lewtas, J. *Rupture of the Pericardium*, Indiana M Gaz 2 296, 1876.

13 Allan, J. *Rupture of the Pericardium, Fracture of the Pelvis and Rupture of the Urethra*, Lancet 2 331, 1878.

cardium it was found to be adherent by its anterior margin, inferiorly the lung was thinned out and insinuated around and behind the apex of the heart. When the adhesions were broken up, the pericardium proper proved to be entirely absent from the left side of the heart, and the internal (medial?) surface of the left lung acted in its place. It was then observed that the anterior margin of the left lung adhered to the retracted right border of the torn pericardium. The left side of the lacerated pericardium appeared as a band $\frac{3}{4}$ inch (1.9 cm) broad, running parallel with the long axis of the body behind the middle part of the heart, and presented a free border. The portion of pleura in contact with the left side of the heart was unaltered. The improvised pericardium contained 1 ounce (30 cc) of turbid serum, with a layer of recent lymph on the heart and parietal surfaces. Concomitant injuries were fractures of the os innominatum, separation of the sacroiliac synchondrosis and rupture of the membranous urethra.

CASE 34—(Reynier¹⁴) In this case trauma to the chest was incurred without injury to the heart, although there was a wide communication between the pericardial sac and one of the pleural cavities. Death took place after three hours.

Comment—After Fischer's⁶ review of the literature, the next one was made by Schuster,¹⁵ in 1880. The following abstracts were obtained from this source, and the references are for the most part as he gave them.

CASE 35—(Biermer *Schweiz Ztschr f Heilk* 2 146, 1863) A 33 year old man was run over by a heavy wagon and died twenty-two hours later. Rupture of the pericardium, a tear in the right auricle, numerous fractures and rupture of the left bronchus were present.

CASE 36—(Bernt *Beit z ges Arzneykunde*, vol 5, p 86) A man of 58 fell from a choir loft, lacerating the pericardium from top to bottom, tearing the right auricle, separating the heart from its great vessels and fracturing the sternum, nearly all the ribs and many other bones.

CASE 37—(Bernt, J *Visa reperta*, Vienna, J B Wallishausser, 1827-1845, vol 3, p 286) In this case a 1 inch (2.5 cm) tear in the pericardium, right atrium and septum, fractures of the arms and several ribs, and rupture of the liver occurred in a 47 year old man as a result of a fall.

CASE 38—(Bernt, J *Visa reperta*, Vienna, J B Wallishausser, 1827-1845, vol 3, p 328) A woman of 70 was run over, as a result there were several tears in the pericardium, rupture of the right atrium, superior vena cava, diaphragm, liver and stomach, and fracture of several ribs and the right clavicle.

CASE 39—(Dehenne, A *Rec d mém de méd mil* 34 377, 1878) Dehenne described a case of rupture of the heart and pericardium in a soldier who fell from a horse and died within an hour. The left arm was broken.

14 Reynier, P. *Recherches cliniques et expérimentales sur le bruit de moulin dans les traumatismes de la poitrine*, Thesis, Paris, no 14, Paris, A Parent, 1880, cited by Martin and Mazel²⁰

15 Schuster. *Ueber die Verletzungen der Brust durch stumpf-wirkende Gewalt, vom gerichtts-arztlichen Standpunkt*, *Ztschr f Heilk* 1 417, 1880

CASE 40—(Maschka, J *Pr Vierteljahrs*, vol 73, p 121) A laborer was crushed between two trains, with resultant fracture of the sternum and all the ribs and rupture of the pericardium, left ventricle and upper lobes of the lungs

CASE 41—(Pamard, cited by Dehenne, A *Rec de mem de med mil* **34** 377, 1878) A man 39 years old was crushed under a heavy load and died immediately The pericardium was ruptured, the right ventricle was torn and many ribs were fractured

CASE 42—(Taylor, A S *A Manual of Medical Jurisprudence*, London, J Churchill, 1844, vol 1, p 639) A child was instantly killed when run over The pericardium and heart were torn for their entire length External signs of injury were absent

CASE 43—(Bernt, J *Beit z ger Arzneykunde*, vol 4, p 100) When pitched from a wagon by a bolting horse, a 48 year old man died immediately Autopsy showed fracture of the sternum, several ribs and one vertebral body and laceration of the pericardium and of both cardiac ventricles

CASE 44—(Bernt, J *Visa reperta*, Vienna, J B Wallishausser, 1827-1845, vol 2, p 314) A man 48 years of age fell from a height, rupturing the pericardium, interatrial septum, lungs, liver and spleen The sternum and several ribs were fractured

CASE 45—(Casper, J L *Practisches Handbuch der gerichtlichen Medicin*, Berlin, A Hirschwald, 1857, vol 2, p 256) This person was run over by a railway train The pericardium and numerous other organs were ruptured, but the heart was spared There were many fractured bones

CASE 46—(Bernt, J *Visa reperta*, Vienna, J B Wallishausser, 1827-1845, vol 2, p 302) A manservant of 44 years was run over The pericardium had a 4 inch (10 cm) tear, the heart was undamaged A bruise was seen on the chest, ribs were fractured and several organs contained lethal ruptures

CASE 47—(Bernt, J *Visa reperta*, Vienna, J B Wallishausser, 1827-1845, vol 2, p 332) A 44 year old man fell from a roof, tearing the pericardium from top to bottom, crushing the skull and breaking several ribs and the sternum

CASE 48—(Gerin-Roze, cited by Dehenne, A *Rec de mem de med mil* **34** 377, 1878) This person fell from a third story, rupturing the heart, aorta and pericardium

CASE 49—(Devergie, M *Medecine legale*, Paris, Germer-Bailliere, 1836, vol 2, p 376) A man of 30 years who had been in a drunken brawl and probably was struck in the chest died quickly as a result of a rent in the pericardium at the root of the great vessels and rupture of the intrapericardial portion of the pulmonary artery There was a stab wound in the neck

CASE 50—(Rose,¹⁶ 1884) This author saw 2 patients with traumatic injury of the chest resulting in combined rupture of the heart and pericardium, 1 patient lived four days and the other for several hours

¹⁶ Rose, 1884, cited by Loison *Rev de chi* **19** 49, 1899, cited by Bright, E F, and Beck, C S *Non-Penetrating Wounds of the Heart A Clinical and Experimental Study*, *Am Heart J* **10** 293, 1935

CASE 51—(O'Brien,¹⁷ 1893) A woman fell 8 feet (244 cm) into the water and was struck by a ship's propellor. Examination disclosed ecchymoses over the chest, fracture of the sternum between the fourth and fifth ribs and a transverse laceration of the heart and pericardium. The ribs were uninjured.

CASE 52—(Hutchinson,¹⁸ 1894) A man of 59 was kicked in the chest by a horse, and a precordial hematoma developed. The skin was unbroken. Signs of severe shock were evident, and death ensued after four hours. Autopsy revealed no fracture of the sternum or ribs, the anterior mediastinum was filled with blood clot which had issued from a rent in the front part of the pericardium, a second tear communicated with the pleural cavity. The heart was not displaced and appeared to have stopped in diastole. At the apex of the right ventricle was a rupture less than $\frac{1}{4}$ inch (0.6 cm) in diameter. Beneath the epicardium between the rupture and the ventricular septum, was a small ecchymosis. Hutchinson said he thought that the pericardial rupture by preventing tamponading of the heart delayed death.

CASE 53—(Bergmann,¹⁹ 1901) A young man was apparently crushed between two railroad cars and died en route to the hospital. To the left of the sternum was an abrasion a few centimeters in extent. The left pleural cavity contained clotted blood. None of the bones of the thorax were fractured. The pericardium was torn, and the heart, which had herniated through the rent, lay in the left pleural sac. Both ventricles were torn at the base, the auricles were also open, and the organ remained attached only to the great vessels. The other organs were said to have been uninjured.

CASE 54—(Martin and Mazel,²⁰ 1914) A man was found lying on a railway track. He was semicomatose or unconscious and died after three days. Subcutaneous emphysema developed over the upper part of the thorax. The presence of premastoid ecchymosis led to the suspicion that the skull was fractured. No attention seems to have been paid to the pulse or to the heart. When the sternum was removed, the pericardium was seen to be torn through the whole left lateral line and anterior to its insertion in the diaphragm, some vestiges of the latter remaining in the form of dark ecchymotic areas. The posterior surface at the level of the interpulmonary area was intact. Of the anterior surface, only a strip remained, covering just the right auricle and ventricle, this had a much heavier consistency than normal pericardium, the free end was frayed and fringed. In addition to the traumatic lesions, inflammation, evidenced by fibrinous exudate in typical *cor villosum* arrangement, existed both over and beneath the lacerated pericardium. Fibrinous pleuritis complicated multiple perforating fractures of the sixth to the ninth left ribs. The heart and lungs had escaped traumatization.

17 O'Brien, C. M. Traumatic Rupture of the Heart Consequent on Fracture of the Sternum, *Brit. M. J.* 2 843, 1893.

18 Hutchinson, F. Case of Traumatic Rupture of the Heart, *Brit. M. J.* 2 1427, 1894.

19 Bergmann. Ein Fall von subkutaner traumatischer Ruptur des Herzens und Herzbeutels, *Monatschr. f. Unfallh.* 8 15, 1901.

20 Martin, E., and Mazel, P. Un cas de déchirure traumatique du péricarde sans lésion du cœur avec pleuro-péricardite consecutive, *Arch. d'anthropol. crim.* 29 754, 1914.

CASE 55—(Kellert,²¹ 1917) A man aged 44, an Italian, was buried up to the waist in a sand bank cave-in. Necropsy, eight days later, revealed five small abrasions on the left anterior part of the chest. The sternum and ribs were intact. The right pleural sac was obliterated by old adhesions. The left lower part of the pericardium presented a ragged opening 4 cm in diameter, the pericardial sac was filled with clotted blood and communicated with the left pleural cavity. The heart lay to the left of the midsternal line and was twisted slightly from left to right. There was a large amount of firm blood clot adherent to the anterior and right lateral surfaces, near the apex on the right posterior surface was a ragged linear laceration of the heart, with blood-stained margins, allowing free communication with both ventricles.

CASE 56—(Doughty,²² 1923) A housewife 35 years of age had been knocked down by an automobile four days previously. She sought attention because of dyspnea when lying down. Choking and a sensation of fulness in the hypochondrium while eating were additional complaints. Physical examination showed pronounced orthopnea without cyanosis. The apex beat was in the sixth interspace 4 cm to the right of the midline. The left cardiac border was 2 cm to the left of the midline. A systolic murmur was audible over the apex. The pulse rate was 120 and the blood pressure 132 systolic and 84 diastolic. Inspection of the thorax showed limited movement of the left side. The left dome of the diaphragm was elevated 3 cm and had respiratory excursion of 3 cm, in contrast to that of 6 cm on the right side. Fluoroscopic examination confirmed the existence of dextrocardia, although the aortic arch was in the normal location. After a week of observation, with progressive discomfort, laparotomy was attempted under local anesthesia, but the patient soon became unmanageable and expired suddenly as chloroform inhalation was begun.

At postmortem examination a linear tear of the right side of the pericardium was found, and through this the heart protruded into the right pleural cavity. A fibrinous exudate was present between the epicardium and the pleura. The left leaf of the diaphragm was ruptured, and through it the stomach and some of the small bowel protruded into the pleural cavity. The condition of the ribs and sternum was not mentioned but in a personal communication to us (Aug 30, 1937) Doughty stated that he was certain none of the ribs were fractured.

CASE 57—(Haberda,²³ 1927) Two cases were mentioned, that of an infant of 8 months (the mother had jumped with the baby from a third story window to the pavement below) and that of a woman of 34 who had thrown herself from the second floor. The thoracic wall of the infant was not injured, the pericardial laceration was located on the anterior surface and was accompanied by hemorrhage into the mediastinum. In the woman both the sternum and the heart were uninjured, there was no hemorrhage into the mediastinum and only the internal layer of the pericardium was torn.

21 Kellert, E. Traumatic Rupture of the Heart. Report of a Case with Uninjured Chest Wall, *J Lab & Clin Med* 2 726, 1917.

22 Doughty, J F. Traumatic Rupture of the Pericardium with Resulting Dextrocardia Complicated by Rupture of the Diaphragm and Liver, *J A M A* 81 1784 (Nov 24) 1923.

23 Haberda, A, in von Hofmann, E. *Lehrbuch der gerichtlichen Medicin*, ed 11, Berlin, Urban & Schwarzenberg, 1927, p 584.

CASE 58—(Spitzmuller,¹ 1928) A janitor 40 years old fell 15 meters through a skylight, striking on the sacrum. Consciousness was retained, he was shocked and complained of excruciating pain in the chest and abdomen and painful respiration. The pelvis and knee joints showed evidences of injury, but the chest did not. Results of physical examination were otherwise unimportant. The temperature rose to 38.5 C, the pulse maintained a rate of 160 to 170. Rigidity and tenderness of the upper part of the abdomen led to laparotomy on the second day, nothing was found. On the third day pain, radiating to the left shoulder, first appeared, what seemed to be rapidly advancing pneumonia developed, and he died that day.

Pertinent necropsy findings were contusion of the left pectoral muscle and rupture of the pericardium on the left side with extrusion of the heart. The tear extended to within 3 cm of the apex of the heart, and over the pericardial surfaces fibrin had been deposited. There was no blood staining of the pericardium. Congenital absence of the membrane was excluded by dissections demonstrating a normal course of the phrenic nerve. There was no mention of fractures of the sternum or ribs. Spitzmuller reasoned that rupture of the pericardium had been brought about by indirect trauma. In so doing he apparently overlooked the evidence of injury to the left pectoral muscle.

COMMENT

Since the publication of the first account of traumatic rupture of the pericardium, in 1706, this has been a well recognized type of injury. Even so, but little attention has been given the matter, as evidenced by the few and widely scattered references in the literature over a period of more than two hundred years. In this connection it is interesting to note the changing nature of the causative agents. Formerly the victims were struck by wagon tongues, run over by wagons or kicked by horses, at present, keeping pace with the machine age, the great majority are killed by automobiles.

From the standpoint of symptomatology the literature offers two points worthy of consideration. Both Allan¹³ and Spitzmuller¹ mentioned the intense precordial pain, temporary in the first instance and constant in the second. Doughty's patient, although lacking angina, had marked cardiac embarrassment, which, however, could have been due in part to the diaphragmatic hernia. Our case is somewhat like Allan's, in that pain was present for a time and later disappeared. On the other hand, according to Kosmin,²⁴ an isolated wound of the pericardium not involving the blood vessels may be practically asymptomatic, because the pericardium as such does not give rise to pain and an injury to it need not necessarily be associated with a change in cardiac activity. Like Doughty's subject, ours died suddenly after a latent period, although from a different cause than his. A second observation, appar-

²⁴ Kosmin, V. P. Mechanism of the Origin and Differential Diagnosis of Wounds of the Pericardium Without injury to the Heart, *Novy khir arkhiv* 32: 129, 1934.

ently long overlooked but of diagnostic importance, is the "water wheel murmur" heard and described by Lavallee in 2 proved instances of traumatic pericardial rupture. In the presence of such a sound the differential diagnosis lies between a traumatically produced pericardio-pleural communication and pneumohydropericardium.

Although not proved by necropsy, the case reported by William Stokes²⁶ was probably an example of pericardial rupture. Clinically, the report was splendidly prepared, and for this and the further reason that the original is not readily accessible, we feel justified in summarizing the paper.

Mr B, aged 21, had been in good health until 1822 (nine years before), when, while playing in a large water wheel, he was thrown on his face by the revolving wheel and caught half in and half out of the wheel in a line running from the inferior angle of the left scapula to the top of the right shoulder. With the next turn of the wheel he fell into the water, was rescued immediately and remained unconscious for three hours. On examination two lower ribs on the left side, the right clavicle, the humerus and the fifth to seventh ribs on the right side proved to be fractured. The right side of the face and thorax were emphysematous. There was complete paralysis of the right arm, with some loss of sensation. Subjectively there was great pain in the right side of the chest, giving the sensation of a foreign body which prevented respiration into the right lung. The pain was accompanied by a violent throbbing and heaving, and it was soon discovered that the heart was pulsating at the right side of the sternum. There was a short, dry cough but no hemoptysis.

Treatment consisted of bleeding and other measures. In two days the emphysema subsided. For the next month he was in bed, still suffering from a dry cough and pain in the side. The following month he was ambulatory. For the next eighteen months he experienced frequent recurrences of pain, which were invariably treated with the lancet. The function of the paralyzed arm gradually returned. The heart continued to pulsate on the right side, and the cough persisted being aggravated by winter weather and by exercise. During several winters there were attacks of an "inflammatory nature" in which he suffered from violent pain in the right side of the chest, palpitation and marked dyspnea. These were always relieved by bleeding (about fifty times) without syncope, even when 30 ounces (890 cc) of blood was taken. In 1829 he began taking digitalis, with considerable relief, and gradually increased the dose to 6 to 8 grains (0.39 to 0.5 Gm) of the powder at a single dose, without untoward symptoms or a decrease of the pulse rate below 80. When first examined by Stokes the man was free from symptoms and appeared to be in good health. There was depression of the right shoulder, an increase of about an inch (2.5 cm) in size was noted in the lower right side of the chest, the left side sounded clear, respirations were of the puerile type, and the sounds could be heard over the normal cardiac region, the sounds of the heart being imperceptible over the lower part of the chest and barely audible superiorly. The upper portion of the right lung was clear to the level of the fifth rib, but from there to the base it was completely dull. The

25 Footnote deleted

26 Stokes, W. A Case of Probable Dislocation of the Heart from External Violence, *Edinburgh M & S J* 36:45, 1931, *London M Gaz* 8:560, 1831.

cardiac pulsation could be seen and felt in the right mammary region between the sixth and seventh ribs within an inch of the sternum. There were no signs of valvular disease.

Stokes said he felt that only traumatic rupture of the pericardium with displacement of the heart could account for the findings. His differential diagnosis included consideration of congenital malposition, extensive left pneumothorax, tumor of the left side of the thoracic cavity, extensive empyema, emphysema, herniation of viscera through the diaphragm and aneurysm of the abdominal aorta. In support of the diagnosis of traumatic pericardial rupture he stressed the insistence of the patient that previous to the accident he had often felt his heart pulsating in the normal position and was the first to point out to friends that the pulsation had shifted to the right side of the sternum after the accident. This ruled out the probability of congenital malposition of the heart. The finding of resonance and breath tones by percussion and auscultation satisfied Stokes that pneumothorax or tumor was not present. He employed the same argument against diaphragmatic hernia and in summarizing stated:

We must admit then that this is an example of dislocation of the heart with rupture of the pericardium and right pleura, a supposition which appears to me to agree perfectly with the history of the case and the state of the patient. From the history it appears probable that the patient has suffered repeated attacks of pleuritic inflammation of the right lung. But the most singular circumstance connected with this extraordinary case is the fact that the patient after so dreadful an accident, lived so long and enjoyed a tolerable state of existence.

If one could only be certain that a ruptured pericardium was responsible for the signs and symptoms, this case would be the most remarkable of its kind on record. To us it appears that diaphragmatic hernia was not adequately ruled out.

Another equivocal case is that described by Cameron.²⁷

A man 67 years of age died of bronchopneumonia and dilatation of the heart without any physical signs pointing to the existence of the extensive pericardial defect discovered at necropsy. Five years before death the man had fallen a distance of 17 feet (5 meters) through a hatchway, sustaining numerous and serious injuries that rendered him unable to perform physical work thereafter. Positive necropsy evidences of the accident were sharp kyphosis of the spine at the level of the eleventh and twelfth thoracic vertebrae, with compensatory lordosis at the sixth dorsal body, severe right lateral scoliosis, absolute rigidity of the spine from the fifth dorsal vertebra caudally, deformities of the ribs resulting from the curvatures of the spine and a long scar in the right lobe of the liver anteriorly, with adhesion to the abdominal wall. Between the sternum and the pericardium were dense fibrous adhesions. The parietal pericardium was represented by only a pouchlike structure on the right and inferior aspect of the heart,

²⁷ Cameron, A. L. Defects of the Parietal Pericardium, *Tr. Chicago Path Soc.* 9: 148, 1914.

the left side of the organ was entirely devoid of pericardial covering. The sac was about one-half the size of the heart and of sufficient size to accommodate the right auricle and about half of the ventricle. It resembled closely a normal pericardium through which a section had been made passing just to the left of the pulmonary artery and missing its attachments to the diaphragm on the left side by a distance of about 2 cm, the plane of the section being at right angles to the vertical plane of the body. Posteriorly the pericardium was represented by a narrow band of tissue 2 cm at its greatest width and becoming narrowed as it ascended until it was cordlike and measured about 0.5 cm at the junction with the pulmonary artery. The free left margin of the pouch was sharply defined except for a distance of about 7 cm on the left inferior margin, where a flap of thin fibrous tissue, heavily laden with fat, was prolonged and lay free on the diaphragm. Inferiorly and posteriorly this flap was continuous with the pericardial sac. The fibrous pericardium was normal, save for several marked prolongations of fat-filled fibrous tissue which were present on its anterior aspect. The serous lining of the pouch was normal throughout.

Cameron reviewed only the literature on congenital pericardial defects. In the discussion he mentioned that the fall, with positive evidences of injury still remaining at the time of death, may have caused the heart to rupture through a comparatively normal pericardium. He likewise considered the possibility of a lesion partly congenital and partly traumatic, with enlargement of a congenital opening due to trauma. In conclusion he stated that the lack of other adhesions, and especially the free, rounded, fatty margin of the remaining pericardial folds, made it impossible to conclude that the defect was not congenital. There was no mention of the location or state of the phrenic nerves, so that this cannot be employed as evidence for or against either type of defect. The reader will not fail to see certain points of similarity between this case and our extraordinary one. If trauma was the cause of the pericardial lesion, Cameron's case is even more remarkable than ours with respect to the period of survival.

A point of parallelism between Allan's case and ours is the well defined retraction of the divided pericardium. Morel-Lavallée, Martin and Mazel, Doughty, Spitzmuller and possibly Reynier made similar observations. Any one who has seen Beck's²⁸ excellent motion pictures taken during operations on the heart can readily understand the mechanism of pericardial retraction and cardiac extrusion, for the movements and contortions of the heart held in restraint are most vigorous and it requires no imagination to visualize how such an organ may easily work its way through even a comparatively small opening in the pericardium and even bring about the purse string effect we have described.

²⁸ Beck, C. S. Noble Wiley Jones Lectures of the University of Oregon Medical School, 1937.

The fact that a number of patients have survived pericardial rupture for an appreciable time confirms the already well known fact that the pericardium is not an indispensable structure. While in certain of the cases on record pericarditis was present, this has been clearly related to trauma and hemorrhage and not to pulmonary infection. According to Southworth and Stevenson,²⁹ the spread of infection from the lungs or pleura to the exposed epicardium is the greatest single menace to the person with a congenitally defective pericardium. Our youngest subject escaped this complication either because of not having pneumonia between the date of the accident and the date of death or because the heart was not laid bare by retraction of the pericardium.

Lavallée appears to have been the first to attempt to explain the mechanics of pericardial rupture. It was his belief that when the heart and lungs are crushed against the vertebral column during an impact, tearing of the pericardium is produced by shearing or rubbing of the membrane against the bone. Later Lavallée, in discussing another case, stated that rupture might be produced by vibration, but again mentioned friction as a possibility.

Much later Spitzmuller postulated that force applied to the body, even if not directly on the chest, might be transmitted and produce a pendulum-like swing of the heart of sufficient magnitude so that the impact of the organ against the pericardium might cause it to rupture. It appears to us that an essential part of such a concept is the unwarranted assumption that the left border of the pericardium is weaker than other parts of it.

Certain facts demonstrated by our own series of cases of pericardial rupture as well as many of those reported in the literature are opposed to Spitzmuller's theory. First, it is hard to conceive of the possibility of any long sweeping motion of a structure so well stabilized against appreciable lateral motion by the short caval and pulmonary veins as the heart without laceration or actual rupture of one or more of these structures. While some of our patients displayed injury to the intra-pericardial veins, we have not found it in the absence of fracture of the ribs in locations where damage by them offered the best explanation for injury of the vessels. In such cases we have ascribed the pericardial rupture to the same cause. Second, it is difficult to imagine that the heart, moving for such a short distance as it would within a previously normal pericardial sac, could attain enough momentum to rupture a relatively strong and fibrous sheath like the pericardium. Third, this theory fails to explain the relatively frequent rupture of the right side of the pericardium or of the anterior or posterior aspect. Fourth, Spitzmuller failed to take into account the almost constantly present

29 Southworth, H., and Stevenson, C. S. Congenital Defects of the Pericardium, *Arch Int Med* 61:223 (Feb) 1938

evidences of injury to ribs or the thoracic wall in situations indicating that the impact was in an anteroposterior direction, wherein a pendulum motion of the heart could scarcely be imagined. Finally, in Spitzmuller's own subject there was hematoma beneath the pectoralis muscle, plainly indicating that trauma was applied directly to the chest and not, as he seems to have believed, indirectly in such a manner that the heart swung laterally in pendulum fashion with sufficient force to tear the sac about it.

With only slight modification it appears to us that the concept originally stated by Lavallée and so convincingly proved by Beck " as operating in traumatic rupture of the heart itself will also apply to the pericardium. Even in the absence of perforation or laceration of the pericardium due to fracture of the sternum or ribs, the following chain of events might logically be expected. 1. Forcible compression of the thorax occurs with at least momentary springing of the ribs and resultant deformity of the bony cage. 2. At the moment of maximum intensity of the externally applied force and its resultant compression, the heart may be caught between the anterior thoracic wall and the spine posteriorly, as Lavallée and Beck have shown. We feel, however, that instead of rubbing or shearing the pericardium, as Lavallée suggested although this may be the mechanism at times, it is more likely that if the point of maximum intensity is broad enough, the result may be complete closure of the pericardial space at one point. If this happens to be over the heart itself, the organ within the closed-off portion of the sac may act as a fluid mass under tension and with the rapidly encroaching pressure may produce a relatively high internal expanding force within a fibrous membrane generally admitted to be melastic when quickly stretched. These are essentially the conditions existing in a bag filled with water and squeezed from the top. At some point the pressure thus applied is sufficient to rupture the fabric. It is also comparable to the manner in which rupture or herniation of the sheath of the biceps brachialis muscle takes place. The site of pericardial rupture depends on several factors, e. g., the greatest free area or surface on which the expanding pressure is exerted, the direction of the applied force (the point where the sac is closed off), the direction from which the force is applied and, finally, the side of the spine to which the heart is shifted or slides when it is compressed. Thus, if the force is directed to the right anterolateral aspect of the chest, the heart would tend to be caught on the right side of the vertebral column, and the hydrostatic pressure would be exerted on its right border, if rupture took place, it would be there. In a similar manner, rupture of the left side of the organ could be brought about. The greater frequency of tears on the left side of the pericardium may be due to the fact that this is the largest free area and in this way possibly a site of weakness. The concept

advanced will also explain the reason why most ruptures occur on the side corresponding to the point of applied force

We are acutely aware of the role of fracture of the ribs or sternum in the production of wounds of the pericardium and apply this hypothesis only to those instances in which there are no concomitant fractures, to ruptures of the pericardium in places where penetration by the ends of the ribs could not explain the rupture or to tears which are not of the puncture type and not associated with wounds of the myocardium. Such instances, especially in immediately fatal injuries, are by no means infrequent. The patients in our series who displayed tearing of the inferior vena cava, a finding that in our opinion would almost of necessity accompany the "pendulum swing" of the heart postulated by Spitzmuller as a cause of pericardial laceration, showed fractured ribs in situations that would readily explain the damage sustained by the vena cava.

An apparent exception to the rule that direct trauma of the chest may cause pericardial rupture is Kelleit's²¹ case, concerning which he offers two possible explanations

first, that the weight of the falling earth, which being soft and adaptable, caused equal pressure over the chest resulting in great compression and bursting of the heart, very much as though a rubber bag distended with fluid were compressed at its middle. To obtain such an effect without fracture of the sternum or ribs seems very unlikely. The second and more probable explanation is that of hydraulic pressure. The large quantity of sandy soil exerted such great pressure over the lower half of the body as to drive most of the blood out of the vessels. This produced sudden over-distention of the heart, which was probably dilated as a result of physical exertion, with consequent rupture at several points. That the force was a great one is indicated by the ruptured pericardium and hemorrhages in the lung.

Despite every effort to discover all previous reports of pericardial rupture it is likely that some ruptures, particularly in association with traumatic rupture of the heart and not indicated in the titles, have been overlooked.

SUMMARY

Traumatic rupture of the pericardium is not, as the literature indicates, a rare occurrence. It is no doubt encountered as frequently in every series of autopsies on persons dying as a result of trauma as it has been in our series.

Commonly, pericardial rupture is merely one of many injuries and in most instances contributes little or nothing to the cause of death. One may rightly anticipate therefore that few examples of long survival will ever be recorded.

The pertinent data in 22 cases found among 4,107 consecutive and unselected cases studied at autopsy have been tabulated and evaluated. Among these, 1 case stands out conspicuously, not only in our group

but among all others on record, because of the fact that the child survived for two and one-half years and, further, because of the singular mechanism responsible for the sudden death. This case is described in detail.

The views of others and ourselves as to the mechanical principles involved in the production of pericardial rupture are given.

Since previous writers, other than Fischer (1868) and Schuster (1880), have not done so, we have attempted to collect and abstract all the literature on the subject. The majority of the earlier reports were available to us only through the articles by Fischer and Schuster. Including our 22 examples, the total number of reported cases now stands at 80.

NOTE—Since the acceptance of the present study there has come to our attention the monograph by Erik Warburg, entitled "Subacute and Chronic Pericardial and Myocardial Lesions Due to Nonpenetrating Traumatic Injuries. A Clinical Study" (translated by H. Andersen and G. Seidelin, London, Oxford University Press, 1938).

A careful check of the text and bibliography of this excellent work fails to disclose additional instances of pericardial rupture.

Of interest in connection with our singular case is Warburg's statement that even sudden and surprising death occurring a long time after the trauma may be of traumatic origin (page 89).

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XIII A SUMMARY OF THE EFFECT OF WHOLE LIVER, WHOLE
MEAT, EXTRACTED LIVER AND EXTRACTED MEAT DIETS
ON RENAL HYPERTROPHY, RENAL FUNCTION, BLOOD
PRESSURE AND CARDIAC HYPERTROPHY

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The effect of diet on the function of the normal and the abnormal kidney has not been agreed on by experimental workers or clinicians. Reports from this laboratory have shown that renal hypertrophy, renal function, cardiac hypertrophy and blood pressure in intact and in partially nephrectomized rats are affected by diets containing varying concentrations of whole meat, extracted meat, whole liver and extracted liver. The purpose of this paper is to present a summary and comparison of these results obtained with the various diets¹

The experimental methods and the results have been presented in detail². The whole and the water-extracted meat and liver were dried and incorporated in balanced experimental diets. All animals chosen

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1 The diets are abbreviated as follows: whole meat, M, extracted meat, EM, whole liver, L, and extracted liver, EL, the numbers following these letters designate the percentage concentration of the respective materials in the diet. The $\frac{\text{heart weight}}{\text{surface area}} \times 100$, $\frac{\text{kidney weight}}{\text{surface area}} \times 100$, $\frac{\text{liver weight}}{\text{surface area}} \times 100$ represent the weight of tissue per hundred square centimeters of surface area and are designated as $\frac{H}{S} \frac{W}{A}$, $\frac{K}{S} \frac{W}{A}$ and $\frac{L}{S} \frac{W}{A}$, respectively. The percentage of nitrogen in the respective diets is shown in table I.

2 (a) Chanutin, A., and Ferris, E. B., Jr. Experimental Renal Insufficiency Produced by Partial Nephrectomy. I. Control Diets, *Arch. Int. Med.* **49**: 767 (May) 1932. (b) Chanutin, A. III. Diets Containing Whole Dried Liver, Liver Residue and Liver Extract, *ibid.* **54**: 720 (Nov.) 1934. (c) V. Diets Containing Whole Dried Meat, *ibid.* **58**: 60 (July) 1936. (d) Chanutin, A., and Ludwig, S. XI. Diets Containing Dried Extracted Liver, *ibid.* **64**: 513 (Sept.) 1939. (e) XII. Diets Containing Dried Extracted Meat, *ibid.* **64**: 526 (Sept.) 1939.

for these analyses were fed the experimental diets from a minimum of seventy-five to a maximum of one hundred and seventy-five days

KIDNEY WEIGHT

Intact Animals—The average kidney weight per hundred square centimeters of surface area for intact rats is presented in table 2. It is seen that the $\frac{K}{S} \frac{W}{A}$ ratios for the rats fed the whole meat diets tend to be smaller than those for rats on the remaining diets at the respec-

TABLE 1—Percentage of Nitrogen Content in the Rations

Diet	Nitrogen	Diet	Nitrogen	Diet	Nitrogen	Diet	Nitrogen
M 10	1.7	EM 10	1.9	L 10	1.4	EL 10	1.5
M 20	2.8	EM 20	3.1	L 20	2.2	EL 20	2.9
M 40	5.2	EM 40	5.5	L 40	4.4	EL 40	5.1
		EM 60	8.4	L 60	6.2	EL 60	7.2
M 80	10.0	EM 80	11.1	L 80	8.2	EL 80	9.6

TABLE 2—The Effect of Diet on the Kidney Weight per Hundred Square Centimeters of Surface Area of Intact and of Partially Nephrectomized Rats*

Protein Component, %	Average Kidney Weight, Mg			
	Diet M	Diet EM	Diet L	Diet EL
Intact Rats				
10	358 (1.0)	416 (1.0)	362 (1.0)	390 (1.0)
20	426 (1.19)	441 (1.06)	388 (1.07)	413 (1.06)
40	442 (1.23)	491 (1.18)	495 (1.37)	450 (1.15)
60		525 (1.26)	498 (1.38)	520 (1.33)
80	500 (1.40)	625 (1.50)	604 (1.67)	535 (1.37)
Partially Nephrectomized Rats				
10	182 (1.00)	229 (1.00)	166 (1.00)	222 (1.00)
20	245 (1.35)	311 (1.36)	266 (1.60)	304 (1.37)
40	318 (1.68)	385 (1.68)	438 (2.64)	388 (1.75)
60		433 (1.89)	459 (2.76)	510 (2.30)
80	410 (2.26)	547 (2.39)	537 (3.24)	532 (2.40)

* The figures in parentheses represent the relative increases in kidney weight when the 10 per cent protein component is considered as 1.0

tive levels of protein ingestion. It is also seen that there is a progressive increase in the size of all kidneys with increasing concentration of protein, but that the kidney weight per unit of the protein component is different for each dietary group. An analysis of renal hypertrophy on the basis of the nitrogen content of the diet yields similar results. Since the total solids of the kidneys of intact animals are found to be constant, the hypertrophy changes represent increases in kidney tissue.

Partially Nephrectomized Animals—The values in table 2 for the partially nephrectomized rats show a progressive increase in the wet weight of the kidney stumps per unit of surface area with increasing

increments of protein in the diet. These values are not representative of true renal hypertrophy, owing to the wide variation in water content. The dried kidney weights available for the animals fed the EM and the EL diet, however, indicate that the proportionate increases in the $\frac{K}{S} \frac{W}{A}$ ratios for the wet kidney weights are approximately correct. It is noted that the greatest range in values was obtained for the animals fed the whole liver diets.

If the average $\frac{K}{S} \frac{W}{A}$ ratios for the intact and for the partially nephrectomized rats on the diets containing 10 per cent protein is considered as 1, the comparative increases in renal hypertrophy can be obtained. It is seen that the ratios for animals fed the M, the EM and the EL diet are quite similar. This is surprising in view of the rather wide differences in the absolute values of the respective $\frac{K}{S} \frac{W}{A}$ ratios. Since there is a comparatively marked increase in the ratios of the animals fed whole liver diets, it follows that increasing amounts of water-soluble liver extractives affect the degree of renal hypertrophy markedly. It is difficult to estimate by either morphologic or functional studies how much of the hypertrophic substance in the kidney stump is due to inactive connective or degenerated tissue.

RENAL FUNCTION

Concentration Test—Intact Animals. The urinary volumes and specific gravities of the intact animals were not affected by the different diets. Low urinary volumes and high specific gravities were obtained consistently.

Partially Nephrectomized Animals. The average values for urinary volumes, specific gravities and proteinuria for the rats fed the M, the EM and the L diet are summarized in table 3. These average values are presented to show the general trend of the effects of diets, although the individual variations are too large to attempt a statistical analysis. In general, a maximum increase in urinary volume and proteinuria and a maximum decrease for specific gravity was reached with each diet when the concentration of the protein component reached 40 per cent. The more concentrated protein diets caused negligible additional changes.

Urea Ratio—Intact Animals. The average values for the urea ratio ($\frac{\text{urea excreted per hour}}{\text{urea in 100 cc blood}} \times 100$) of intact rats on the whole meat, the extracted meat and the extracted liver diets are summarized in table 4. There is a progressive increase in the values for the urea ratios with an increase in the amount of protein ingested with the exception of those for the group fed the EL 80 diet. The low value for this group may indicate renal damage. Furthermore, the urea ratios at the

respective levels of protein ingestion are quite similar, indicating that the type of protein is not an important factor in determining the degree of clearance

The urea clearance per gram of kidney is given by the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio and thus eliminates the factor of renal hypertrophy. The average values for these ratios are unusually constant for practically all diets

TABLE 3—*Effect of Diet on the Average Values of Urinary Volume, Specific Gravity and Protein Excretion During a Concentration Test on Intact and on Partially Nephrectomized Rats*

Protein Component, %	Diet M	Diet LM	Diet L
Volume of Urine (Cc)			
10	4.6 (2.6)	5.8 (1.9)	3.5 (1.4)
20	8.0 (2.7)	9.5 (3.1)	6.5 (2.9)
40	12.4 (3.1)	13.5 (2.0)	13.3 (3.1)
60		11.3 (2.6)	11.0 (2.4)
80	11.7 (2.6)	10.7 (2.8)	12.5 (2.6)
Specific Gravity (Corrected)			
10	1.0250 (1.0433)	1.0289 (1.0500)	1.0340 (1.0495)
20	1.0247 (1.0493)	1.0242 (1.0480)	1.0326 (1.0532)
40	1.0207 (1.0513)	1.0197 (1.0601)	1.0207 (1.0524)
60		1.0210 (1.0598)	1.0243 (1.0522)
80	1.0209 (1.0516)	1.0207 (1.0501)	1.0211 (1.0561)
Urinary Protein (Mg)			
10	29	53	15
20	83	96	116
40	133	111	128
60		103	119
80	142	99	74

* The figures in parentheses represent average values for intact rats

TABLE 4—*Effect of Diet on the Average Values of the Urea Ratios in Intact Rats*

Protein Component, %	Diet M	Diet FM	Diet EL
10	70	47	44
20	60	58	55
40	62	60	60
60		64	68
80	66	71	58

(table 5). It is seen that 11 of the 14 average values are within a range of 36 to 38. The values for the animals fed the EL 80 and the EM 80 diets are lower.

It has been demonstrated that renal hypertrophy and the urea ratio are generally increased following the ingestion of diets high in protein. The direct relation between the size of the kidneys and their function in the intact animal is demonstrated by the constancy of the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio. This is a rather remarkable finding in view of the wide variety of diets fed these animals. There is no direct evidence available for explaining the low ratios obtained for the animals receiving the EM 80

and the EL 80 diet. In view of the facts presented, it must be assumed that an increase in renal activity due to excretion of metabolites is accompanied by an increase in the size of the kidneys and in renal function in the intact animals. These changes, however, do not affect the volume or the specific gravity of the urine collected during a concentration test.

Partially Nephrectomized Animals The percentage incidence of the urea ratio values at different levels is presented in table 6. Ratios about 30 are considered to be within the normal range, and renal insufficiency becomes progressively greater with the lower ratios. It

TABLE 5—*Effect of Diet on the Average Values of the $\frac{\text{Urea Ratio}}{\text{Kidney Weight}}$ Ratios in Intact Rats*

Protein Component, %	Diet M	Diet EM	Diet EL
10	36	36	39
20	37	37	38
40	36	37	38
60		37	38
80	28	32	33

TABLE 6—*Effect of Diet on the Percentage Distribution of the Urea Ratios of Partially Nephrectomized Rats*

Protein Components, %	Urea Ratio Range											
	Above 30 Diet			30-15 Diet			15-5 Diet			5-0 Diet		
	M	EM	EL	M	EM	EL	M	EM	EL	M	EM	EL
10	3	2	0	58	43	21	39	19	76	0	6	3
20	0	0	0	42	21	43	55	71	48	3	8	9
40	0	0	0	11	11	25	68	70	63	21	19	12
60		0	0		30	34		60	59		10	7
80	0	2	0	27	29	52	60	69	42	13	0	6

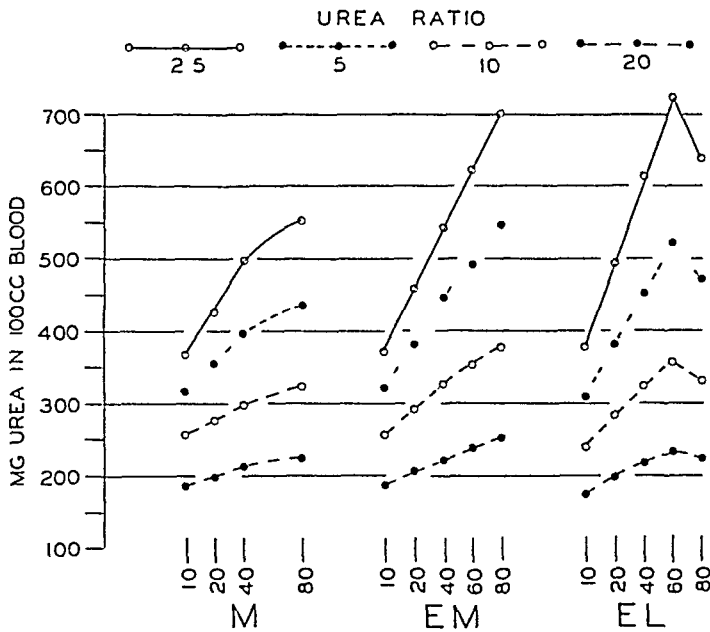
is seen that few partially nephrectomized animals have normal renal function. The greatest incidence of marked renal insufficiency, as judged by the percentage of animals with ratios below 15, was noted in the groups fed diets containing 40 per cent protein. The results of the concentration test appear to confirm the observations obtained with the urea clearance tests.

The accompanying chart illustrates the relation between the urea ratio and the concentrations of blood urea with the different diets. For a given urea ratio, the concentration of the blood urea is lowest for the group ingesting whole meat. The values are higher for the animals fed the extracted meat and the liver diets. They increase rapidly with an increase of protein content in the diet at any given ratio, except for an unexplained definite decrease in this relation in the group receiving the EL 80 diet.

BLOOD PRESSURE AND HEART WEIGHT

Intact Animals—The blood pressures of the intact animals were quite constant, and the majority were between 120 and 130 mm of mercury. The $\frac{H}{S} \frac{W}{A}$ ratios were found to be variable, but the majority remained within a limited range.

Partially Nephrectomized Animals—The effect of diet on the percentage distribution of blood pressures at selected levels is shown in table 7. The group of rats on the diets of extracted meat had the greatest incidence of hypertension (above 160 mm). It is difficult to explain the difference between the animals on the M 10 and the



Relation between urea ratio and concentrations of blood urea

EM 10 diet, since the incidence of hypertension was 14 and 52 per cent, respectively. The difference in these two diets is in the small amount of water-soluble extractives. It is striking that there is such a marked difference in the percentage incidence of hypertensive animals in the group fed the M and the EM diet and the groups fed the L and the EL diet at the 80 per cent protein level. The type and amount of protein in the diet unquestionably exerts a definite effect on blood pressure.

The correlation coefficients for the $\frac{H}{S} \frac{W}{A}$ ratios and blood pressures are summarized in table 8. It is noted that the highest degree of correlation was uniformly obtained with diets containing 10 per cent protein. Of the values for the 19 diets, those for only 3 (EM 60, EM 80 and L 60) show a lack of correlation. A further analysis undertaken to determine the correlation coefficients for each diet gave

the following values whole meat, 0.61 ± 0.034 , extracted meat, 0.57 ± 0.020 , whole liver, 0.67 ± 0.03 , and extracted liver, 0.73 ± 0.02 . These data demonstrate that there is a substantial or marked relation between the degree of hypertension and the degree of cardiac hypertrophy.

The Value of the $\frac{H \cdot W}{S \cdot A}$ per Unit of Blood Pressure—In order to judge the efficiency of heart muscle, the milligrams of heart per hundred square centimeters of surface area were calculated for each 10 mm of mercury blood pressure according to the formula $\frac{H \cdot W / S \cdot A}{\text{blood pressure}}$.

TABLE 7—*Influence of Diet on the Percentage Distribution of the Blood Pressures at Different Levels*

Protein Component, %	Blood Pressure Range											
	100-140 Mm Diet				140-160 Mm Diet				Above 160 Mm Diet			
	M	EM	L	EL	M	EM	L	EL	M	EM	L	EL
10	49	29	60	51	37	19	22	22	14	52	18	27
20	47	36	40	22	26	24	30	27	27	51	30	51
40	24	16	32	46	37	29	32	26	39	56	36	28
60		17	33	28		36	33	42		47	29	30
80	31	26	53	49	34	38	30	39	35	37	17	12

TABLE 8—*Correlation Coefficients and Probable Errors Between $\frac{H \cdot W}{S \cdot A}$ Ratio and Blood Pressure of Partially Nephrectomized Rats*

EL 10	0.76 ± 0.04	EM 10	0.67 ± 0.05	M 10	0.73 ± 0.049	L 10	0.89 ± 0.029
EL 20	0.49 ± 0.03	EM 20	0.52 ± 0.06	M 20	0.68 ± 0.056	L 20	0.67 ± 0.033
EL 40	0.59 ± 0.06	EM 40	0.60 ± 0.06	M 40	0.42 ± 0.035	L 40	0.41 ± 0.11
EL 60	0.44 ± 0.03	EM 60	0.14 ± 0.10			L 60	0.17 ± 0.11
EL 80	0.49 ± 0.09	EM 80	0.33 ± 0.07	M 80	0.61 ± 0.036	L 80	0.66 ± 0.105

The average data for the intact and for the partially nephrectomized rats are presented in table 9. It is evident that heart weights of both the intact and the partially nephrectomized rats were affected. Since the blood pressures of intact rats remained fairly constant regardless of diet, the differences in the heart weight per unit of blood pressure must be related to the dietary regimen. The average values for each group of animals were not affected by the concentration of protein fed. It is seen that the ratios for both the intact and the partially nephrectomized animals fed the EM and the EL diet are definitely smaller than those for the animals fed the M and the L diet. A statistical analysis was made to determine if there was a significant difference between the average values for intact and for partially nephrectomized rats on the same diet; positive differences were obtained for 13 of the 19 diets.

Despite the differences in the distribution of hypertensive animals in the various groups, hypertension appears to have practically no effect on the average ratios. Furthermore, a study of the ratios of individual animals indicates that the degree of hypertension does not necessarily determine the decreased values obtained for partially nephrectomized animals. It would seem that renal insufficiency per se influences the amount of cardiac tissue per unit of blood pressure.

SUMMARY

Diets containing protein components varying from 10 to 80 per cent of whole meat, extracted meat, whole liver and extracted liver,

TABLE 9—*Influence of Diet on the Milligrams of Heart per Hundred Square Centimeters of Surface Area for each 1 Mm. of Blood Pressure*

Diet	Intact Rats	Partially Nephrectomized Rats
EM 10	1.29 \pm 0.022	1.21 \pm 0.020
EM 20	1.31 \pm 0.020	1.21 \pm 0.022
EM 40	1.27 \pm 0.019	1.16 \pm 0.018
EM 60	1.24 \pm 0.018	1.11 \pm 0.028
EM 80	1.31 \pm 0.019	1.17 \pm 0.017
Average	1.28	1.17
EL 10	1.27 \pm 0.015	1.26 \pm 0.023
EL 20	1.33 \pm 0.019	1.27 \pm 0.024
EL 40	1.34 \pm 0.022	1.22 \pm 0.018
EL 60	1.33 \pm 0.018	1.19 \pm 0.023
EL 80	1.26 \pm 0.018	1.15 \pm 0.022
Average	1.31	1.22
M 10	1.43 \pm 0.045	1.34 \pm 0.026
M 20	1.48 \pm 0.031	1.33 \pm 0.026
M 40	1.42 \pm 0.036	1.27 \pm 0.023
M 80	1.39 \pm 0.033	1.29 \pm 0.041
Average	1.43	1.31
L 10	1.45 \pm 0.03	1.42 \pm 0.027
L 20	1.60 \pm 0.047	1.38 \pm 0.037
L 40	1.58 \pm 0.041	1.40 \pm 0.043
L 60	1.59 \pm 0.057	1.41 \pm 0.044
L 80	1.50 \pm 0.047	1.37 \pm 0.033
Average	1.54	1.39

respectively, have been fed for periods of from seventy-five to one hundred and seventy-five days to intact and to partially nephrectomized rats. The effect of these diets on renal hypertrophy, renal function, blood pressure and cardiac hypertrophy has been studied with reference to the amount and type of the protein component in the diet.

In the intact rat each increment of the protein component generally caused a progressive renal hypertrophy and an increase in the urea clearance. Variations in the protein content did not affect the volume or specific gravity of the urine obtained during a concentration test with a twenty-four hour specimen. The blood pressures and the size of the hearts were not appreciably affected by augmenting the protein components. The main effect of the type of protein component was

manifested by the larger amount of heart muscle per unit of surface area required to maintain a given blood pressure in the animals on the whole meat and the whole liver diets

In the partially nephrectomized animals the effect of increasing the protein component of the diet on renal hypertrophy was similar to that in the intact animals. Urinary volumes, proteinuria, hyposthenuria and a decrease in urea clearance were progressive with protein increments of from 10 to 40 per cent, but further increments caused no further constant effect on the measure of renal function. The type of the protein component appeared to influence the incidence of hypertensive rats, particularly in the group fed the extracted meat diets. The values for the heart weight per unit of surface area for a given blood pressure were significantly smaller for the partially nephrectomized rats than for the intact rats on the same diet.

CONCLUSIONS

It appears from these experiments that the concentration of the protein in the diet has a greater effect on the function of the normal and the abnormal kidney than the type of the protein component.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

XIV DIETS CONTAINING WHOLE DRIED YEAST

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Numerous workers¹ have reported that the administration of yeast extracts to white rats is effective in preventing renal hypertrophy caused by excessive ingestion of protein. There are no data showing the possible relation between the size and the function of the kidneys under such conditions. This investigation was undertaken to study the effect of feeding diets containing varying concentrations of dried yeast on renal hypertrophy, renal function and blood pressure in intact and in partially nephrectomized rats.

EXPERIMENTAL METHODS

The details of the procedures for the care of the animals and for determining the blood pressure and renal function have been presented in previous papers.² Eighty to 90 per cent of the total kidney tissue was removed by a two stage operation from the partially nephrectomized rats.

Five experimental diets were used and were designated as Y 20, Y 30, Y 40, Y 60 and Y 80 according to the percentage of dried yeast which they contained. The composition of the diets is shown in table 1. The experimental period lasted for about one hundred days with a maximum and minimum of one hundred and eight and ninety-five days, respectively.

The ratio of the weight of the heart and kidneys to surface area is expressed by $\frac{H}{S} \frac{W}{A}$ and $\frac{K}{S} \frac{W}{A}$, respectively. The surface area was calculated from the weight of the animal by the formula of Lee.³

The dried yeast was contributed by Standard Brands, Inc.

From the Laboratory of Physiological Chemistry, the University of Virginia.

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¹ Longwell, B. B., Johnston, R. P., and Hill, R. M. *J. Nutrition* **12** 155, 1936.

² Chanutin, A., and Ludwig, S. Experimental Renal Insufficiency Produced by Partial Nephrectomy. V. Diets Containing Whole Dried Meat, *Arch. Int. Med.* **58** 60 (July) 1936.

³ Lee, M. O. *Am. J. Physiol.* **89** 24, 1929.

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls—A summary of results, including surface area, blood pressure, $\frac{H}{S} \frac{W}{A}$ and $\frac{K}{S} \frac{W}{A}$ ratios, total solids of the kidneys, urea ratio and $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio, respectively, for intact rats is presented in table 2

The individual and mean values for blood pressure are greatest for the group receiving the Y 20 diet and least for the group receiving the Y 80 diet. The values for the rats receiving the Y 30, the Y 40 and the Y 60 diet are fairly constant. Of the 69 blood pressure values, 2 are above 150 mm and 3 above 140 mm of mercury. With these few exceptions, the yeast diets exerted no significant influence on the blood pressure of intact rats.

The $\frac{H}{S} \frac{W}{A}$ ratios for the group fed the Y 20 diet are slightly greater than those for the remaining groups. The relation between blood

TABLE 1—Composition of Experimental Diets

Diet	Concentration of Component in Diet, Percentage					
	Yeast	Starch	Lard	Cod Liver Oil	Salt Mixture*	Nitrogen Content
Y 20	20	54	17	5	4	19
Y 30	30	44	17	5	4	25
Y 40	40	34	17	5	4	33
Y 60	60	14	17	5	4	47
Y 80	80	5	6	5	4	60

* Osborne and Mendel²

pressure and $\frac{H}{S} \frac{W}{A}$ is extremely constant for all the control animals.

The mean values for $\frac{K}{S} \frac{W}{A}$ ratios are constant for the rats fed the Y 20, the Y 30 and the Y 40 diet, which indicates failure of the kidneys to hypertrophy with increased ingestion of protein. There was, however, an appreciable renal hypertrophy in the animals fed the Y 60 and the Y 80 diet. These relations are presented more accurately in chart 1, in which the individual values of $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios are shown.

The individual values for the urea ratios vary markedly and depend on the kidney weight. This is shown by the constancy of the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios, which average 36, 35, 41, 40 and 36 for the respective yeast diets, beginning with the Y 20.

Partially Nephrectomized Rats—The effects of the Y 20, the Y 30, the Y 40 and the Y 60 diet on partially nephrectomized rats are shown

TABLE 2—*Observations on Control Animals Fed a Variety of Diets*

Renal Condition and Diet	Value	Duration of Experi- ment, Days	Surface Area	Blood Pressure, Mm	Heart Weight		Kidney Weight		Total Solids of the Kid- neys, %	Urea Ratio	Urea Ratio	
					Surface Area × 100	Weight	Surface Area × 100	Weight			Kidney Weight	Weight
2 kidneys Y 20	Minimum	103	354	126	0.164	0.386	0.386	0.386	24.5	39	27	27
	Maximum	103	441	156	0.200	0.427	0.427	0.427	26.2	70	41	41
	Average	103	395	133 ± 3.33	0.178 ± 0.008	0.405 ± 0.004	0.405 ± 0.004	0.405 ± 0.004	25.1	77 ± 3.5	36	36
	Rats	9	9	9	9	9	9	9	9	9	9	9
2 kidneys Y 30	Minimum	96	308	114	0.132	0.261	0.261	0.261	24.2	42	25	25
	Maximum	118	480	131	0.183	0.465	0.465	0.465	26.5	88	14	14
	Average	105	404	125 ± 1.59	0.161 ± 0.003	0.415 ± 0.006	0.415 ± 0.006	0.415 ± 0.006	25.7	78 ± 4.7	35	35
	Rats	16	16	16	16	16	16	16	16	10	10	10
2 kidneys Y 40	Minimum	96	283	102	0.143	0.346	0.346	0.346	22.9	51	36	36
	Maximum	103	444	151	0.188	0.478	0.478	0.478	26.8	82	51	51
	Average	100	370	124 ± 2.74	0.165 ± 0.003	0.412 ± 0.009	0.412 ± 0.009	0.412 ± 0.009	25.2	66 ± 3.6	41	41
	Rats	17	17	17	17	17	17	17	9	9	9	9
2 kidneys Y 60	Minimum	98	345	112	0.151	0.409	0.409	0.409	23.8	49	31	31
	Maximum	99	440	142	0.171	0.550	0.550	0.550	26.9	99	50	50
	Average	99	384	127 ± 2.63	0.161 ± 0.005	0.473 ± 0.010	0.473 ± 0.010	0.473 ± 0.010	25.7	73 ± 3.87	40	40
	Rats	14	14	14	14	14	14	14	14	14	14	14
2 kidneys Y 80	Minimum	102	244	94	0.134	0.410	0.410	0.410	22.0	48	23	23
	Maximum	105	394	132	0.182	0.648	0.648	0.648	25.6	105	48	48
	Average	103	326	111 ± 2.9	0.162 ± 0.004	0.564 ± 0.020	0.564 ± 0.020	0.564 ± 0.020	23.9	70 ± 5.3	36	36
	Rats	13	13	13	13	13	13	13	13	10	10	10

in tables 3 to 6, respectively. Charts 2 to 6 were prepared from these tables to facilitate comparisons of the effect of different diets on the blood pressure, kidney weight and renal function. Owing to the lack of sufficient yeast, the Y 80 diet was not fed to the partially nephrectomized animals.

Blood Pressure The outstanding effect on blood pressure was found to be the definite increase of hypertensive animals in the group receiving the Y 60 diet. The animals receiving the remaining diets showed only slight changes in the percentage distribution of blood pressures (chart 2).

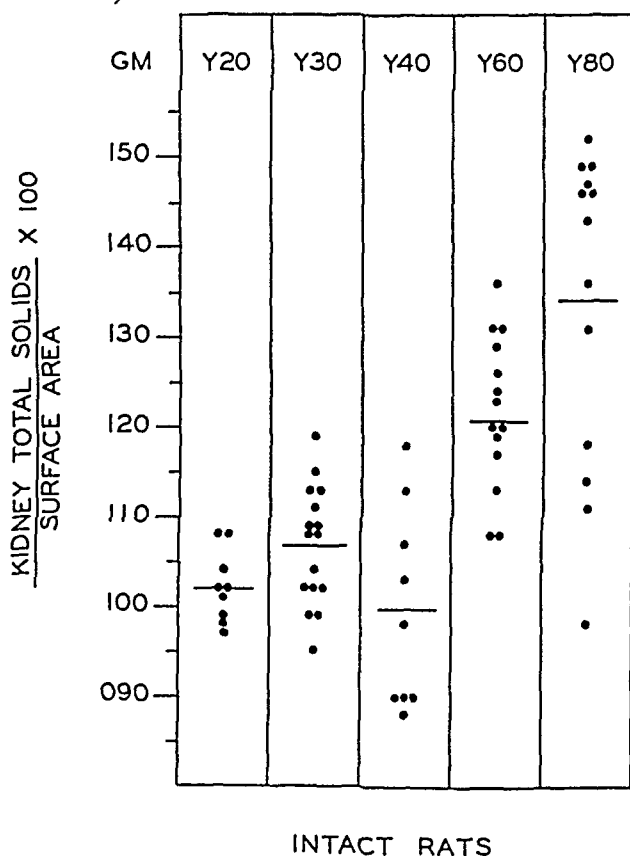


Chart 1—Effect of diet on the solids of the kidneys per hundred square centimeters of surface area in intact rats

It has been well established that there is a fairly substantial relation between the $\frac{H}{S} \frac{W}{A}$ ratio and the height of blood pressure of partially nephrectomized rats. The correlation coefficients and probable errors as calculated for partially nephrectomized rats fed yeast diets follow: Y 20, 0.66 ± 0.058 , Y 30, 0.46 ± 0.113 , Y 40, 0.64 ± 0.072 , and Y 60, 0.65 ± 0.076 . These results indicate that there is a substantial or marked relation between cardiac hypertrophy and blood pressure.

Kidneys The individual values for the $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios are presented in chart 3. There is a progressive increase in the mean weight of the dried kidneys per hundred square centimeters as follows: Y 20,

TABLE 3—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of Kidneys, %	Urea Ratio
				Surface Area × 100	Surface Area × 100		
1	95	291	176	0 199	0 198	20 8	13
2	95	232	210	0 232	0 175	21 2	8
3	95	276	166	0 221	0 132	20 8	12
4	95	286	136	0 189	0 201	21 6	29
5	95	233	134	0 176	0 183	17 5	9
6	95	274		0 203	0 195	22 4	15
7	95	265	134	0 185	0 201	24 6	24
8	95	289	156	0 189	0 207	23 9	25
9	95	232	216	0 226	0 142	16 1	7
10	95	322	134	0 180	0 215	20 2	23
11	95	278	198	0 171	0 200	20 2	14
12	95	286	176	0 179	0 178	24 4	34
13	95	274	178	0 187	0 191	22 4	22
14	95	270	144	0 199	0 192	24 5	16
15	95	228	136	0 174	0 178	24 8	17
16	95	270	184	0 205	0 194	23 4	19
17	95	268	160	0 195	0 178	25 8	22
18	95	244	170	0 211	0 184	21 8	11
19	95	234	118	0 195	0 189	20 1	7
20	95	272	130	0 172	0 164	24 0	20
21	99	304	136	0 191	0 204	18 9	
22	99	314		0 218	0 242	22 7	9
23	99	283	148	0 190	0 244	21 0	9
24	99	324	154	0 193	0 210	22 9	22
25	99	348	152	0 192	0 214	22 0	24
26	99	289	136	0 175	0 162	21 5	10
27	99	297	146	0 173	0 211	20 3	
28	99	308	144	0 162	0 184	23 2	
29	99	320	146	0 170	0 200	22 0	18
30	99	299	134	0 187	0 208	24 2	
31	99	295	198	0 196	0 252	20 0	12
32	99	272	134	0 172	0 188	23 1	14
33	105	295	148	0 185	0 172	21 6	13
34	105	310	176	0 233	0 223	24 0	24
35	105	220	152	0 170	0 149	21 2	
36	105	270	216	0 241	0 223	19 0	9
37	105	271	196	0 194	0 195	21 4	12
38	105	289	126	0 165	0 178	24 6	22
39	105	306	144	0 173	0 167	23 8	15
40	105	230	106	0 183	0 208	19 2	8
41	105	238	128	0 176	0 153	25 2	21
42	105	274	156	0 186	0 181	21 4	22
43	108	362	152	0 217	0 229	23 0	12
44	108	268		0 179	0 170	21 6	

TABLE 4—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 30 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of Kidneys, %	Urea Ratio
				Surface Area × 100	Surface Area × 100		
1	96	343	128	0 181	0 191	23 4	25
2	96	289	180	0 173	0 282	15 5	5
3	96	328	206	0 243	0 178	19 0	8
4	96	260		0 193	0 192	22 3	13
5	96	268		0 161	0 170	22 7	20
6	96	370	156	0 187	0 186	17 8	22
7	96	386	138	0 183	0 222	23 4	
8	98	274	160	0 157	0 202	23 2	22
9	98	278	123	0 171	0 205	22 7	23
10	98	348	142	0 176	0 227	24 2	27
11	98	328	156	0 175	0 214	21 0	19
12	98	368	206	0 218	0 234	17 4	11
13	98	348	148	0 176	0 243	20 8	13
14	98	310	108	0 244	0 242	20 6	23
15	98	376	108	0 214	0 316	18 9	12
16	98	307	132	0 173	0 215	19 8	12
17	98	360	184	0 280	0 280	16 5	
18	98	297	124	0 203	0 246	21 0	
19	102	306	164	0 190	0 196	22 7	20
20	102	334	170	0 181	0 192	21 4	16
21	102	366	150	0 173	0 215	20 2	23
22	102	412	146	0 174	0 211	21 0	15
23	102	265	190	0 192	0 204	24 3	10

TABLE 5—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of Kidneys, %	Urea Ratio
				Surface Area $\times 100$	Surface Area $\times 100$		
1	97	297	130	0 171	0 233	24 0	32
2	97	286	118	0 165	0 229	22 0	25
3	97	265	134	0 190	0 224	19 0	18
4	97	345		0 248	0 201	16 8	10
5	97	302	154	0 187	0 246	18 4	14
6	97	374	122	0 171	0 222	23 6	25
7	97	426	130	0 194	0 294	22 4	26
8	97	376	152	0 186	0 249	20 9	12
9	102	308	196	0 209	0 336	15 9	10
10	102	383	158	0 168	0 342	18 1	20
11	102	299	164	0 177	0 274	18 7	23
12	102	323	154	0 187	0 279	18 4	21
13	102	280	150	0 201	0 293	18 9	12
14	102	379	138	0 173	0 300	18 9	16
15	102	370	194	0 203	0 378	15 0	
16	102	372	180	0 214	0 366	16 7	12
17	102	360	214	0 232	0 379	14 8	9
18	103	278	128	0 154	0 201	22 2	
19	103	291	158	0 181			
20	103	274		0 153	0 232	22 6	
21	103	265	114	0 153	0 231	21 4	
22	103	280	130	0 148	0 208	23 2	
23	103	265	154	0 164	0 208	22 7	
24	103	272	152	0 178	0 237	20 5	
25	103	297	156	0 177	0 249	21 8	34
26	107	339	156	0 216	0 322	16 5	
27	107				0 250	26 2	26
28	107	301	146	0 161	0 232	23 2	14
29	107	339	180	0 173	0 262	19 3	11
30	107	330	166	0 213	0 310	19 9	14
31	107	345	142	0 162	0 257	24 2	17
32	107	336			0 247	18 7	
33	107	354	160	0 224	0 266	16 9	6
34	107	310	174	0 200	0 202	22 4	5

TABLE 6—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 60 per Cent Dried Yeast*

Rat	Duration of Experiment, Days	Surface Area, Sq Cm	Blood Pressure, Mm	Heart Weight	Kidney Weight	Total Solids of Kidneys, %	Urea Ratio
				Surface Area $\times 100$	Surface Area $\times 100$		
1	97	308	144	0 187	0 304	22 0	10
2	97	307	156	0 181	0 354	18 2	12
3	97	292	176	0 216	0 292	17 5	10
4	97	295	176	0 207	0 315	16 4	11
5	97	341	176	0 212	0 440	16 4	15
6	97	334	140	0 183	0 382	16 9	10
7	97	307		0 191	0 478	14 3	9
8	97	316	174	0 181	0 247	16 0	
9	97	308	214	0 226	0 367	15 9	10
10	97	302	206	0 218	0 335	14 9	15
11	97	348	126	0 163	0 314	20 7	9
12	97	328	160	0 174	0 326	17 2	17
13	97	291	212	0 236	0 339	12 7	5
14	97	320	186	0 201	0 507	13 4	9
15	97	299	148	0 253	0 321	16 4	
16	104	318	166	0 198	0 320	19 2	13
17	104	322	210	0 256	0 288	15 3	11
18	104	316	138	0 218	0 340	15 5	9
19	104	324	180	0 202	0 328	17 4	12
20	104	306	182	0 200	0 325	16 2	9
21	104	356	186	0 225	0 446	15 0	9
22	104	280	166	0 234	0 354	13 7	6
23	104	360	132	0 183	0 392	17 5	18
24	104	340		0 196	0 312	20 0	20
25	104	280	210	0 231	0 485	12 4	9
26	104	330	142	0 169	0 352	20 2	13
27	104	339	146	0 183	0 394	17 1	11
28	104	339	138	0 177	0 294	20 3	15

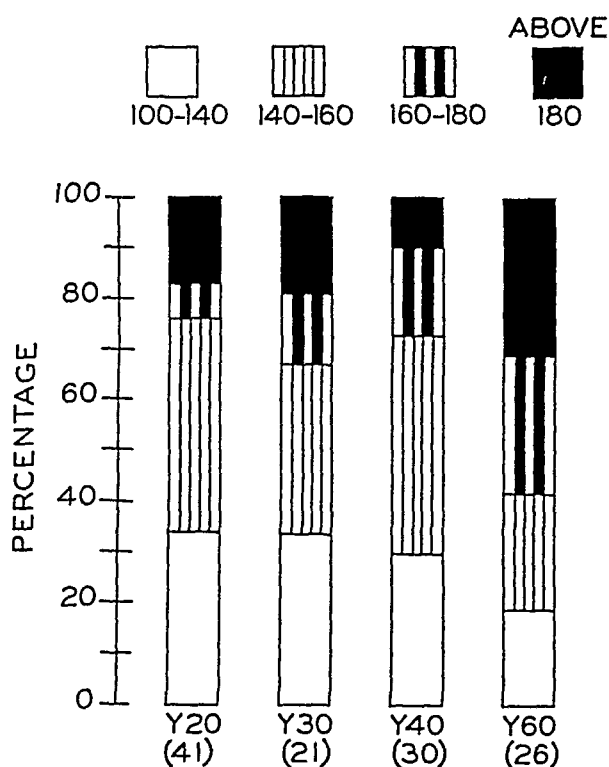


Chart 2—Effect of diet on the blood pressure of partially nephrectomized rats. The figures in parentheses in this and in similar charts indicate the number of animals.

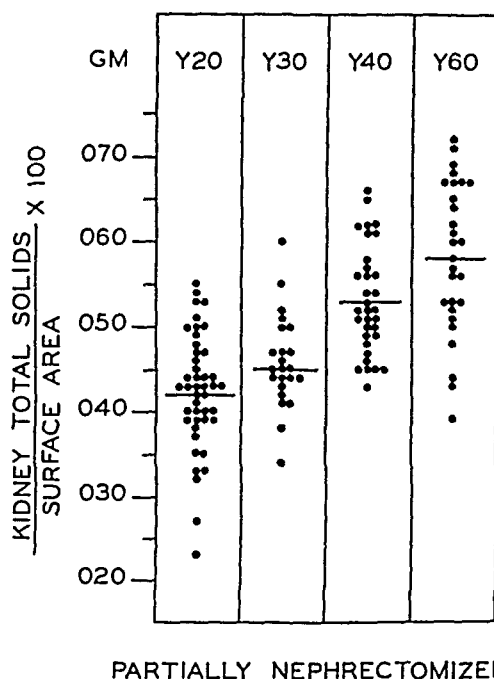


Chart 3—Effect of diet on the solids of the kidneys per hundred square centimeters of surface area in partially nephrectomized rats.

42 mg , Y 30, 45 mg , Y 40, 53 mg , and Y 60, 58 mg If the average value for the group fed the Y 20 diet is considered as 1, the ratios for the respective diets are 1.0, 1.07, 1.26 and 1.38. Apparently yeast does not prevent renal hypertrophy of the kidney remnant as it does for the intact kidneys.

Urea Ratio The percentage distribution of urea ratios at different levels is shown in chart 4. The complete absence of ratios below 5 in this entire series is unusual and striking. There is little difference in the distribution of the ratios for the animals fed the Y 20, the Y 30 and the Y 40, but there is a definite increase in the ratios with values between 5 and 15.

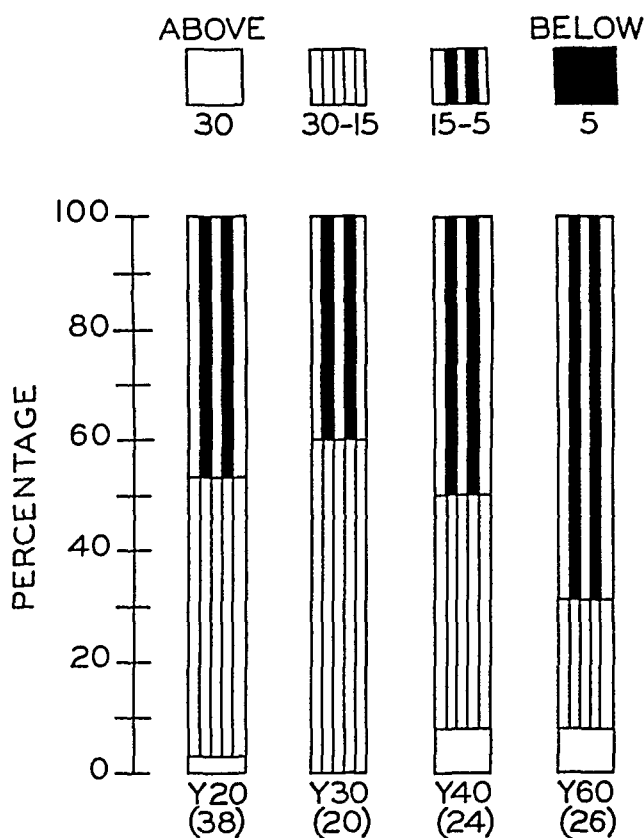


Chart 4—Effect of diet on the urea ratio of partially nephrectomized rats

The Effect of Diet on the Blood and Urine Urea—The adjusted curves and then formulas, obtained by methods previously described, showing the effect of dried yeast diets on the amount of urea in the blood and the urine in relation to the urea ratio of control and experimental rats are shown in chart 5. It is seen that with progressively increased ingestion of yeast there is a greater increase in the concentration of blood urea and a proportionately smaller increase in the concentration of urine urea at any given urea ratio. These increased values represent retention of nitrogen and the inability to excrete administered urea properly.

The effect of diet on the concentration of blood urea at different urea ratios in percentage of mean normal is shown in chart 6. It is striking that there is only a comparatively small difference in the concentration of blood urea at a urea ratio as low as 5 for the different diets.

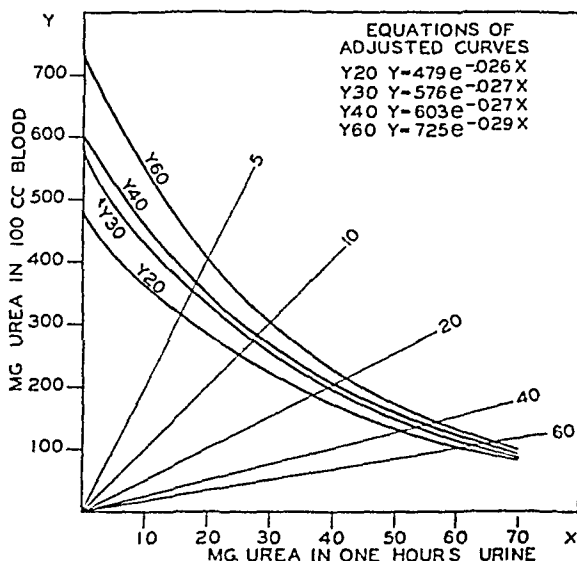


Chart 5—Relation of the adjusted curves for blood urea and urine urea

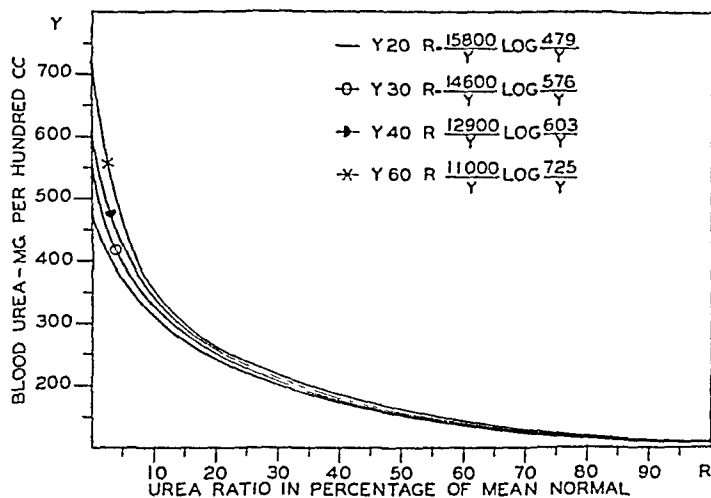


Chart 6—Relation between the concentration of urea in the blood and the urea ratio in percentage of the mean normal value

COMMENT

Longwell and his co-workers¹ have reviewed the effect of yeast concentrates on renal hypertrophy produced by diets high in protein (casein). There is general agreement that there is a prevention or inhibition of renal hypertrophy with these extracts, which appear to be

rich in the vitamin B complex. In the present experiment yeast served both as a source of protein and as the inhibiting factor concerned in renal hypertrophy. The results obtained confirm previous workers so far as preventing renal hypertrophy in intact animals with diets containing comparatively small amounts of yeast.

The inhibiting factor must be considered in relation to the protein fed. Casein has been used by most investigators and is recognized as the least nephrotoxic protein for rats. Whole dried liver, which is rich in the vitamin complex, causes a progressive increase in the size of the kidney with increased concentration in the diet. When the yeast concentration of the diet increases markedly, there is no longer any inhibition in the size of the kidneys of intact rats. Since it has been demonstrated that diets rich in nucleic acid⁴ and phosphates⁵ may be nephrotoxic in the rat, it may be that these factors may be operative in counteracting the effect of the "inhibiting" factor.

In the partially nephrectomized rat, the total solids of the kidney stump increase progressively with increased ingestion of yeast. Since it is impossible to determine accurately the increase in connective tissue in these kidneys, one cannot judge the effect of the "inhibitory" substance on the functioning kidney units.

If the effect of yeast diets on the concentration of urea in the blood and the urine is taken as an index of renal function, it will be seen that there are no urea ratios below 5 for the entire series. This is unusual, since ratios of this magnitude and smaller are obtained for partially nephrectomized animals fed other diets. Furthermore, this is reflected in the relatively low concentrations of blood urea obtained at different urea ratios. If these results are accepted as indexes of renal function, diets containing yeast are relatively less nephrotoxic to rats than such foodstuffs as dried meat, liver, extracted meat or extracted liver.

SUMMARY

The effect of feeding diets containing various percentages of dried yeast to intact rats (20, 30, 40, 60 and 80 per cent) and to partially nephrectomized rats (20, 30, 40 and 60 per cent) has been studied.

Data showing the effects of these diets on renal hypertrophy, renal function and blood pressure in intact rats are presented. There was no change in the $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios for the animals ingesting the diets containing 20, 30 and 40 per cent yeast, but there was a relatively marked increase in the ratios for the animals receiving the Y 60 and the Y 80 diet, indicating that yeast contains substances capable of

4 Newburgh, L. H., and Johnston, M. W. *J. Clin. Investigation* **10** 153, 1931.

5 MacKay, E. M., and Oliver, J. *J. Exper. Med.* **61** 319, 1935.

preventing hypertrophy within definite limits of protein intake. The $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios and the blood pressures were fairly constant with all diets.

The following observations were made on the partially nephrectomized rats.

There was a progressive increase in the $\frac{\text{dry kidney weight}}{\text{surface area}}$ ratios with increasing concentration of yeast in the diet. Yeast does not prevent renal hypertrophy of the kidney remnant.

The incidence of hypertension was greatest in the group ingesting the diet containing 60 per cent yeast.

There was no marked renal insufficiency in any of these animals, as judged by the urea ratios. Furthermore, the concentrations of blood urea were not markedly elevated at the lower urea ratios.

AGE, SEX .AND HYPERTENSION IN MYOCARDIAL INFARCTION DUE TO CORONARY OCCLUSION

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For many years coronary occlusion was considered a disease of old age and emphasis was laid on the marked discrepancy in its incidence between the sexes. More recently, as the diagnosis of occlusion has become more precise, there has been an increasing number of reports of its occurrence in persons in the younger age groups and in women as well as men. Conner and Holt¹ and, later, Bean² took into consideration certain factors of age and sex in their discussion of the prognosis and course of the disease.

In view of the extreme importance of coronary occlusion, a large series of cases observed by us has been analyzed with a view to determining the influence of age, sex and hypertension on the incidence and prognosis of the disease as well as on its various clinical manifestations. In addition, particular attention has been paid to the relation of hypertension to age and sex.

MATERIAL

During the past five years, 500 cases of coronary occlusion were studied in the wards and private pavilion of the Mount Sinai Hospital. These were consecutive cases, included regardless of the type of treatment. Approximately 85 per cent of the patients were Jewish because of the predominance of this racial group in the hospital.

In the following analysis are included only cases in which a typical history, electrocardiogram or postmortem confirmation was present. The course of the disease in these cases was observed by us in great detail, both clinically and by laboratory methods.

From the Cardiographic Laboratory and the Medical Services of the Mount Sinai Hospital.

1 Conner, L. A., and Holt, E. The Subsequent Course and Prognosis in Coronary Thrombosis, *Am Heart J* 5:705, 1930.

2 Bean, W. B. Infarction of the Heart. A Morphological and Clinical Appraisal of Three Hundred Cases, *Am Heart J* 14:684, 1937.

OBSERVATIONS

Sex —Of the 500 patients 387, or 77.4 per cent, were men and 112, or 22.6 per cent, were women, a ratio of 3.4:1 (table 1). This is lower than the calculated ratio of 4.6:1 in 2,803 clinical cases cited in the literature, representing a total of 14 series of cases.³ The lowest ratio of men to women in the individual series was 3:1,⁴ and the highest, 13:1.^{3a} The ratio is somewhat lower in series of cases in which necropsy was performed, in 1,241 such cases⁵ it was 3:1. Except for

3 (a) Parkinson, J, and Bedford, D. E. Cardiac Infarction and Coronary Thrombosis, *Lancet* **1** 4, 1928 (b) Levine, S. A. Coronary Thrombosis, *Medicine* **8** 245, 1929 (c) Bramwell, C. Coronary Occlusion, *Brit. M. J.* **1** 681, 1930 (d) Harrington, A. W., and Wright, J. H. Cardiac Infarction. A Study of One Hundred and Forty-Eight Cases, *Glasgow M. J.* **119** 1, 1930 (e) White, P. D., and Bland, E. F. A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis. A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, *Am. Heart J.* **7** 1, 1931 (f) Allen, O. S. Acute Coronary Thrombosis, *Delaware State M. J.* **6** 252, 1934 (g) Riesman, D., and Harris, S. E. Disease of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease, *Am. J. M. Sc.* **187** 1, 1934 (h) Howard, T. Coronary Occlusion, *M. Times & Long Island M. J.* **62** 337, 1934 (i) Willis, F. A. Life Expectancy in Coronary Thrombosis, *J. A. M. A.* **106** 1890 (May 30) 1936 (j) Vander Veer, J. B., and Brown, L. E., Jr. The Diagnosis and Prognosis of Coronary Occlusion. The Electrocardiogram as an Aid, *Pennsylvania M. J.* **39** 303, 1936 (k) Landau, N., cited in Coronary Occlusion, Special Articles (Vienna), *Lancet* **1** 388, 1936 (l) Mullins, W. L. Age Incidence and Mortality in Coronary Occlusion. A Review of Four Hundred Cases, *Pennsylvania M. J.* **39** 322, 1936 (m) Palmer, J. H. The Blood Pressure in the Years Following Recovery from Coronary Thrombosis, *Lancet* **1** 741, 1937 Conner and Holt.¹

4 Bramwell.^{3c} Harrington and Wright.^{3d} Mullins.^{3l}

5 (a) Wearn, J. T. Thrombosis of Coronary Arteries with Infarction of the Heart, *Am. J. M. Sc.* **165** 250, 1923 (b) Warburg, E. J. Ueber den Coronarkreislauf und über die Thrombose einer Coronararterie. Anatomie, Physiologie und Historik, *Acta med. Scandinav.* **73** 425, 1930 (c) Klotz, O., and Lloyd, W. Sclerosis and Occlusion of the Coronary Arteries, *Tr. A. Am. Physicians* **5** 08, 1930 (d) Covey, G. W. Coronary Thrombosis. A Review of Autopsy Findings, *Nebraska M. J.* **15** 466, 1930 (e) Jervell, A. Elektrokardiographische Befunde bei Herzinfarkt, *Acta med. Scandinav.* 1935, supp. 68, p. 1 (f) Lisa, J. R., and Ring, A. Myocardial Infarction or Gross Fibrosis. Analysis of One Hundred Necropsies, *Arch. Int. Med.* **50** 131 (July) 1932 (g) Meakins, J. C., and Eakin, W. W. Coronary Thrombosis. Clinical and Pathological Study, *Canad. M. A. J.* **26** 18, 1932 (h) Barnes, A. K., and Ball, R. G. Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am. J. M. Sc.* **183** 215, 1932 (i) Evans, N., Ambler, A. C., and Dodson, W. Coronary Disease. Its Pathogenesis, *California & West Med.* **38** 98, 1933 (j) Appelbaum, E., and Nicholson, G. H. B. Occlusive Diseases of the Coronary Arteries. An Analysis of the Pathological Anatomy in One Hundred and Sixty-Eight Cases with Electrocardiographic Cor-

two small series^{5c,m} the ratio in the cases reviewed ranged between 5 1 and 1 1 1. It is obvious from these and our own records that women are definitely less susceptible to coronary occlusion than men, but not to the degree formerly believed.

Age—The youngest patient in our series was 27 years of age and the oldest 87. The average age at the time of the initial attack was 54 years, and the average age for all patients, regardless of the attack observed, was 55 years. The first attack occurred most commonly in the sixth decade (50 to 59 years), taking place in this period in 33.7 per cent of the cases (table 1 and chart 1). The order of frequency in the other age groups was as follows: 60 to 69 years, 26 per cent, 40 to 49 years, 25 per cent, 30 to 39 years, 10 per cent, and 70 to 79 years, 5.4 per cent.

TABLE 1—*Sex Distribution in 500 Cases of Occlusion of the Coronary Artery. Clinical Findings in Males and in Females*

	Males	Females
Number	387 (77.4%)	113 (22.6%)
Ratio	3.4:1	
Age 27-39	33 (8.6%)	6 (5.3%)
40-49	85 (21.9%)	20 (17.9%)
50-59	139 (35.9%)	39 (34.9%)
60-69	103 (26.6%)	33 (29.2%)
70-87	27 (7.0%)	10 (8.8%)
Average Age	54.7 years	56 years
Attack 1	226 (58.4%)	71 (62.9%)
2	127 (32.8%)	35 (31.0%)
3	25 (7.2%)	5 (4.4%)
4	4 (1.0%)	0
5	2 (0.5%)	2 (1.7%)
Mortality	108 (28.0%)	26 (23.0%)
Diabetes	26 (6.7%)	30 (26.8%)
Hypertension	219 (56.5%)	90 (80.0%)
Hypertension + diabetes	223 (57.6%)	99 (88.3%)
Enlarged heart	215 (55.5%)	84 (74.3%)
Heart failure (2 to 4+)	195 (50.4%)	67 (59.8%)
Pulmonary edema	56 (14.5%)	23 (20.5%)
Shock	205 (52.7%)	55 (48.7%)

Only 10 patients were under 30 years of age. Three were 80 or more at the time of the initial attack. The foregoing age distribution differs from those reported by Conner and Holt¹ and by Bean,² in the former's series, although the patients in whom the attack occurred in the sixth decade comprised the largest group, the number of attacks occurring in the fifth decade was greater than that of attacks occurring in the

relation in Thirty-Six of These, *Am Heart J* **10** 662, 1935 (k) Saphir, O, Priest, W S, Hamburger, W W, and Katz, L N. Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes (Thirty-Four Cases), *ibid* **10** 567 and 762, 1935 (l) Moritz, A R, and Beck, C S. The Production of a Collateral Circulation to the Heart, *ibid* **10** 874, 1935 (m) Akerson, I B, Dias, J E, Jr, and Monroe, R T. The Incidence of Coronary Artery Sclerosis in the Aged, *New England J Med* **217** 622, 1937 (n) Lyon, R M M. Myocardial Infarction. A Pathologic Study, *Edinburgh M J* **45** 285, 1938 (o) Bean²

seventh, in the latter's series the attacks occurred (in order of frequency) in the seventh, sixth and eighth decades

When the ages at the initial attack in our series are broken into five year periods (chart 2), it is seen that in practically two thirds of

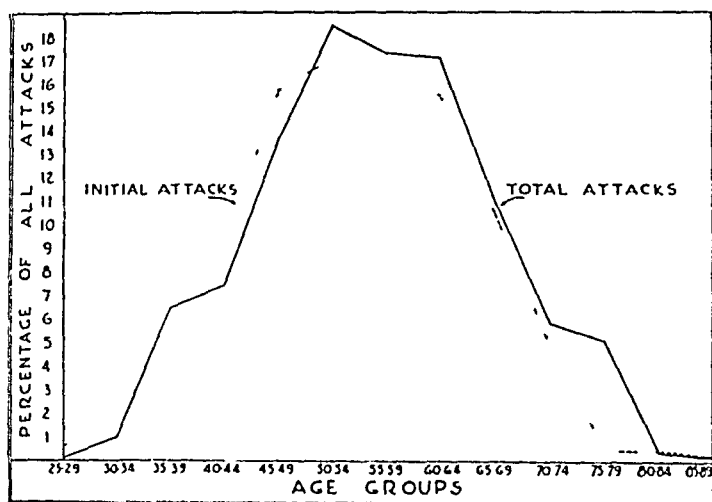


Chart 1—Age incidence in 500 attacks of coronary occlusion

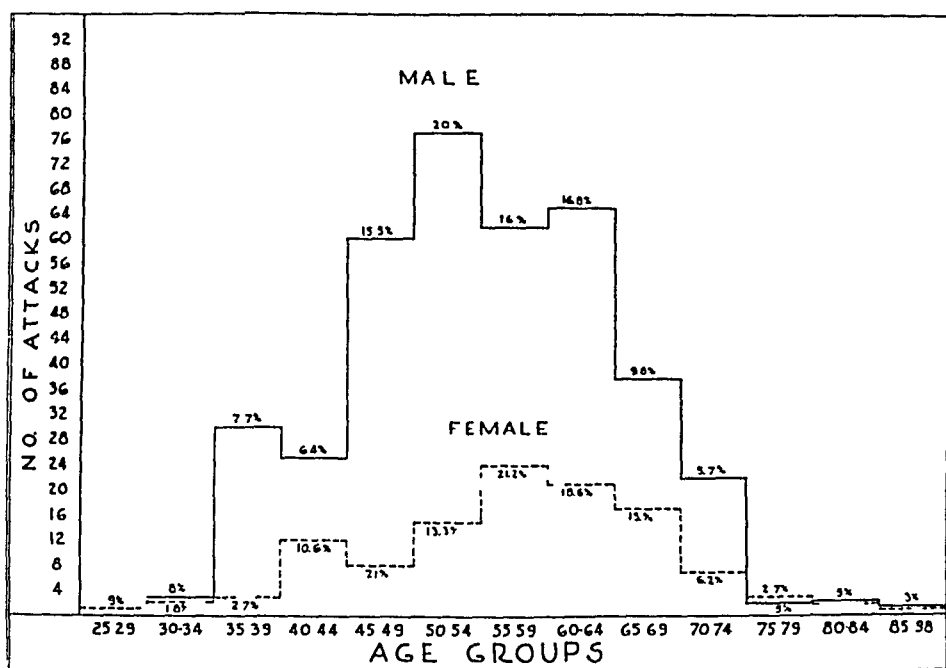


Chart 2—Age and sex incidence in 500 attacks of coronary occlusion

the cases the condition occurred between the ages of 45 and 65 years, with an almost equal division among the four five year periods. In most of the series reported in the literature the condition occurred most frequently in patients aged between 50 and 70 years. In our series the

peak was reached in the 50 to 54 year period and not at 60 years as has generally been believed. Actually, there is a sharp rise at 45 years to an incidence only slightly below the peak, so that the incidence between the ages of 45 and 65 varies little. After the age of 65 there is a sharp drop in the number of patients. One third of the attacks in our series occurred before the age of 50 years and one sixth before the age of 45. Similar conclusions can be drawn if all the cases are considered, including those in which there had been previous attacks except that the number of attacks in the 40 to 49 year period is smaller, i. e., 21 per cent as compared with 24.9 per cent.

When all attacks are considered as against initial attacks alone, there are more patients in the older age groups. The peak still occurs in the sixth decade, which comprises 35.6 per cent of the cases, but the

TABLE 2—Age Distribution in 500 Cases of Occlusion of the Coronary Artery
Clinical Findings in Each Age Group

	Age Group					Total
	27 to 39	40 to 49	50 to 59	60 to 69	70 to 79	
No. of cases	39 (7.8%)	105 (21%)	178 (35.6%)	141 (28.3%)	37 (7.2%)	500
Sex: Male	33 (84.6%)	85 (80.7%)	139 (78.2%)	103 (73.6%)	27 (73.6%)	387 (77.4%)
Female	6 (15.2%)	20 (19.3%)	39 (21.8%)	38 (27.7%)	10 (27.7%)	113 (22.6%)
Attacks: 1	24 (61.5%)	65 (61.9%)	104 (58.4%)	81 (58.6%)	23 (62.2%)	297 (59.4%)
2	13 (33.4%)	33 (31.4%)	55 (30.9%)	48 (34.6%)	10 (27.7%)	162 (32.7%)
3	2 (5.1%)	6 (5.5%)	15 (8.4%)	6 (4.2%)	4 (10.8%)	33 (6.6%)
4	0	1 (1.1%)	2 (1.1%)	1 (0.7%)	0	4 (0.8%)
Mortality rate	6 (15.4%)	22 (20.9%)	43 (24.7%)	60 (42.3%)	13 (36.1%)	144 (28.8%)
Diabetes	2 (5.1%)	5 (3.8%)	19 (10.7%)	20 (14.2%)	10 (27.7%)	56 (11.2%)
Hypertension	14 (36%)	55 (52.2%)	114 (64.6%)	104 (74%)	25 (69.3%)	312 (62.4%)
Enlarged heart	14 (35.9%)	51 (48.6%)	106 (59.5%)	93 (69.5%)	29 (78.3%)	299 (59.8%)
Heart failure, 2 to 4+	12 (30.8%)	48 (45.8%)	83 (46.5%)	83 (59%)	25 (69.3%)	252 (50.8%)
Pulmonary edema	5 (12.8%)	18 (17.1%)	35 (19.7%)	23 (16.7%)	8 (22.2%)	79 (15.7%)
Shock	25 (64.1%)	52 (49.5%)	87 (49%)	77 (54.6%)	24 (64.9%)	263 (52.6%)

number of patients in the seventh decade exceeds that in the fifth (28.3 per cent as against 21 per cent [table 2]). The number of patients in the fourth decade is practically the same as that in the eighth, 7.8 per cent and 7.2 per cent.

These results differ in several respects from those reported in the literature. An analysis of 12 clinical series comprising 1,761 cases^a revealed that the number of attacks in the seventh decade was almost

6 (a) Gordiner, H. C. Coronary Arterial Occlusion, *Am J M Sc* **168** 181, 1924. (b) Christian, H. A. Cardiac Infarction (Coronary Thrombosis) An Easily Diagnosable Condition, *Am Heart J* **1** 129, 1925. (c) Coombs, C. F. Observations on the Etiological Correspondence Between Anginal Pain and Cardiac Infarction, *Quart J Med* **23** 233, 1930. (d) Boas, E. P., and Donner, S. Coronary Artery Disease in the Working Classes *J A M A* **98** 2186 (June 18) 1932. (e) Hochrein, M. *Der Myokardinfarkt Erkennung, Behandlung und Verhütung*, Dresden, Theodore Steinkopff, 1937, p. 4. Conner and Holt¹ Parkinson and Bedford^{2a} Levine^b Bramwell^c Harrington and Wright^d Willhus³ⁱ Palmer^{3m}

as great as in the sixth (32 per cent as compared to 35 per cent), while in five series⁷ the number of attacks occurring in the seventh decade actually exceeded that observed in the sixth. Also, there was a greater number of patients over 70 than of patients below 40, 10 per cent as against 4 per cent. In summary, our series includes more patients in the younger age groups than have been found in previously published studies.

Of particular interest are the patients in our series under 40 years of age, of whom there were 39, or 7.7 per cent. Of these, 1 was 27 years old, 5 were 30 to 34, and 33 were 35 to 39. If the age at the initial attack alone is considered, it is found that 9.4 per cent of attacks occurred before the patient was 40 years old. The diagnosis in 2 cases in which the initial attack occurred before the age of 30 was confirmed by autopsy. In the literature cited, only 106, or 3.3 per cent, of the patients were below 40. However, in addition, 115 attacks of coronary occlusion occurring before the age of 41 have been collected from case reports, both clinical and based on autopsy.⁸ The patients included an

7 Parkinson and Bedford^{3a} Levine^{3b} Christian^{3b} Coombs^{3c} Hochrein^{3c}

8 (a) Osler, W. Disease of the Coronary Arteries, Tr Path Soc Philadelphia **11** 106, 1887-1889. (b) Dreschfeld, J. On Angina Pectoris and Pseudo-Angina, Practitioner **44** 28, 1890. (c) Palmer, W. H. Spontaneous Rupture of the Heart, Boston M & S J **155** 113, 1906. (d) Klingman, T. Spontaneous Rupture of the Heart, New York M J **87** 198, 1908. (e) Gorham, L. W. Significance of Transient Localized Pericardial Friction in Coronary Thrombosis, Albany M Ann **41** 109, 1920. (f) Krumbhaar, E. B., and Crowell, C. Spontaneous Rupture of the Heart, Am J M Sc **170** 828, 1925. (g) Kerr, W. J., Larkey, S. L., and Lassan, A. E. Coronary Occlusion and Myocardial Degeneration, California & West Med **23** 46, 1925. (h) Nathanson, M. H. Disease of the Coronary Arteries, Am J M Sc **170** 240, 1925. (i) Jamison, S. C., and Hauser, G. H. Angina Pectoris in a Youth of Eighteen, J A M A **85** 1398 (Oct 31) 1925. (j) Clark, G. F. Coronary Occlusion, U S Nav M Bull **23** 487, 1925. (k) Benda, C. Ueber einen Fall von schwerer infantiler Koronararteriosklerose als Todesursache, Virchows Arch f path Anat **254** 600, 1925. (l) Allan, G. A. Case Presenting Multiple Arterial Thrombosis Including Both Coronaries, Glasgow M J **110** 351, 1928. (m) Hughes, F. W. T., and Perry, C. B. Senile Arterial Changes in Child Aged Seven Weeks, Bristol Med-Chir J **46** 219, 1929. (n) Herapath, C. E. K., and Perry, C. B. The Coronary Arteries in a Case of Familial Liability to Sudden Death, Brit M J **1** 685, 1930. (o) Werley, G. Coronary Infarct and Angina with Abdominal Symptoms, M J & Rec **131** 367, 1930. (p) Levy, R. L. Mild Forms of Coronary Thrombosis, Arch Int Med **47** 1 (Jan) 1931. (q) Smith, H. L., and Bartels, E. C. Coronary Thrombosis with Myocardial Infarction and Hypertrophy in Young Persons. Report of Two Cases with Necropsy, J A M A **98** 1072 (March 26) 1932. (r) Rathe, H. W. Sclerosis of the Coronary Arteries with Myocardial Infarction in a Young Woman, Am Heart J **9** 539, 1934. (s) Leary, T. Experimental Atherosclerosis in the Rabbit Compared with Human

infant 7 months old, 7 boys and girls aged 10 to 20 years, 8 men and women aged 21 to 30, and 99 patients 31 to 40

A number of authors have observed that women suffer coronary occlusion at a somewhat later age than men⁹ Conner and Holt¹ found that occlusion is uncommon in women under 50 Of the women observed by them, only 19 per cent were under 50, as compared with 35 per cent of the men In Howard's^{3b} series 54 per cent of the women and only 25 per cent of the men were over 60, there were no women under 40 Hochrein's^{6a} patients included 43 men and only 7 women under 50 years but more women than men over 70 Our series shows a similar but less striking difference in this respect We found that 30.3 per cent of the men and only 23 per cent of the women were under 50 Furthermore, 43.4 per cent of the women were 60 years old or over, as compared with 33.6 per cent of the men The discrepancy is even greater below the age of 40 In this group there were 33 men and only 6 women, a ratio of 5.5:1 This observation has been stressed by other writers¹⁰ The average age of the men was 53.5 years for the first attack and 54.7 years for all attacks, while that of the women was 55.7 and 56 years respectively In the series of Levine^{3b} and Mullins³¹ also the average age of the women was two years greater than that of the men The peak incidence among women in our series occurred between the ages of 55 and 59 years, as compared with 50 to 54 years for men

(Coronary) Atherosclerosis, Arch Path **17** 453 (April) 1934 (t) Cullinan, E. R., and Graham, G. Atheroma and Coronary Thrombosis in a Young Diabetic, J Path & Bact **38** 167, 1934 (u) White, P. D. Coronary Disease and Coronary Thrombosis in Youth, J M Soc New Jersey **32** 596, 1935 (v) Sprague, H. B., and Orgain, E. S. Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital, 1914-1934, New England J Med **212** 903, 1935 (w) Cooley, L. E. Longevity After Coronary Thrombosis in a Young Individual, J Iowa M Soc **25** 30, 1935 (x) Fernando, P. B. Coronary Occlusion in a Patient Twenty-Four Years Old, Brit M J **1** 976, 1935 (y) May, W. J. Coronary Infarction in Young Adults, South African M J **10** 772, 1936 (a¹) Glendy, R. E., Levine, S. A., and White, P. D. Coronary Disease in Youth. Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, J A M A **109** 1775 (Nov 27) 1937 (b¹) Burnett, C. T. Pain and Pain Equivalents in Heart Disease, Ann Int Med **10** 1156, 1937 (c¹) Stroud, W. D., in discussion on Glendy, Levine and White^{8a1} (d¹) Halbersleben, D. Coronary Occlusion in a Young Adult, New England J Med **218** 175, 1938 (e¹) Durant, T. M. The Occurrence of Coronary Thrombosis in Young Individuals, Ann Int Med **10** 979, 1937 (f¹) Franklin, M. S. Coronary Thrombosis in Young Adults, J Missouri M A **35** 32, 1938 (g¹) Scott, E. G. Coronary Thrombosis in a Twenty-Seven Year Old Man, Virginia M Monthly **65**:391, 1938

9 Conner and Holt¹ Bean² White and Bland^{3a} Lyon^{5a}

10 Glendy, Levine and White^{8a1} Burnett^{8b1} Stroud^{8c1} Halbersleben^{8d1}

Mortality Rate—We discovered a direct relation between age and mortality rate (table 1 and chart 3) The latter rose from 15.4 per cent in the fourth decade to 42 per cent in the seventh, the average for the entire series being 28.8 per cent It is to be noted, however, that the mortality rate was practically constant between the ages of 40 and 59 years, ranging between 20 and 24 per cent, while at 60 years there was a sharp rise to 42 per cent, which was maintained until 69 years At 70 years and above the rate fell to 36 per cent

A similar trend is observed when the mortality rate for the initial attacks only is considered, the same sharp rise in mortality occurs at the age of 60 The average age was 58 years for the fatal and 53.8 years for the nonfatal attacks It is interesting to note that in the fourth decade the nonfatal attacks were double the number of fatal attacks,



Chart 3—Mortality rate according to age in 500 attacks of coronary occlusion

while in the seventh decade the reverse relation was true A number of authors have remarked similarly on the increasing mortality with age¹¹ and the favorable prognosis for the young¹¹ Willius¹¹ and Mullins¹¹ did not observe one fatality in a patient below the age of 40 In Levine's^{3b} cases of nonfatal occlusion the average age of the patients was 57.8 years, and in his cases of fatal occlusion, 61 years, in Cooksey's¹² series there was an even greater difference, the figures being 54.2 and 63.4 years respectively In several large clinical series the average age was 55.9 years, as against 57.3 obtained in postmortem studies In the latter the highest incidence almost invariably occurred in the 61 to 70 year group and not in patients between 51 and 60 years

11 Bramwell^{3a} Glendy, Levine and White^{8,1} Burnett^{8b,1} Stroud^{8c,1} Halbersleben^{8d,1}

12 Cooksey, W B Coronary Thrombosis Follow-Up Studies with Especial Reference to Prognosis, J A M A **104** 2063 (June 8) 1935

The mortality rate for women in our series was only slightly greater than that for men (32 per cent as against 28 per cent) and the average age of women who died was one year greater than that of men. Willius¹ and Coombs^{6c} found the prognosis poorer for women, but White and Bland^{3e} considered the factor of sex unimportant. The increase in mortality has usually been attributed to the greater incidence of diabetes in women.

Multiple Attacks—The incidence of previous attacks of coronary occlusion was calculated for the patients in each age group. From table 2 it will be seen that the percentage of first, second and third attacks were approximately the same in all decades of life. Fifty-eight to 62 per cent of patients of all ages were treated in their initial attack of occlusion, 31 to 34 per cent of all patients below 70 had suffered at least one previous attack, and 4 to 8.5 per cent, at least two previous attacks. At 70 years and over the incidence of third attacks increased slightly. These figures seem surprising, for one would expect a lower incidence of previous occlusions in the younger age groups. It is apparent, however, that the young patient who has had one attack is as susceptible as the elderly patient to further attacks.

The mortality rate, as was to be expected, increased with each succeeding attack, rising from 23.2 per cent for the initial attack to 35.2 per cent for the second and 39.4 per cent for the third. In each attack, whether the first, second or third, the mortality rate also rose with increasing age.

Diabetes—The incidence of diabetes mellitus in the entire series studied was 11.2 per cent. In patients not previously known to be diabetic the presence of diabetes was determined by observation of persistent glycosuria and hyperglycemia. It is interesting that this incidence in a series drawn from a predominantly Jewish population was similar to that reported by Conner and Holt,¹ whose patients were mainly non-Jewish.

Diabetes was found by us to be more common in the older patients, occurring in 17 per cent of those aged 60 years and older and in only 4.8 per cent of those under 50. Only 2 patients under 40 and only 7 under 50 were diabetic (table 2). These findings are in accord with those of Warren¹³. In his extensive series of diabetic patients, all those who died of arterial degeneration were over 40 years of age and few were under 50.

Diabetes in our series was also much more common in women than in men, the incidence being 26 per cent in the former and only 6.7 per cent in the latter (table 1). The incidence in women rose directly with age.

13 Warren, S. The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930.

from 4.5 per cent in the fifth decade to approximately 50 per cent in the eighth decade. It rose only slightly in males (chart 4).

The prognosis of the attack in diabetic persons was less favorable than for nondiabetic persons, the mortality rate being 39.3 per cent in the former and 27.5 per cent in the latter. In women the discrepancy was even more marked, the mortality rate for diabetic and for nondiabetic persons being 40 and 22 per cent respectively.

It is clear from these data that diabetes was not a factor in the occurrence of coronary occlusion in men and in young women but that it played a definite role in women over 50 years of age. It is evident from the higher mortality rate that the degree of disease of the coronary arteries in patients with diabetes was greater and the clinical course more severe.

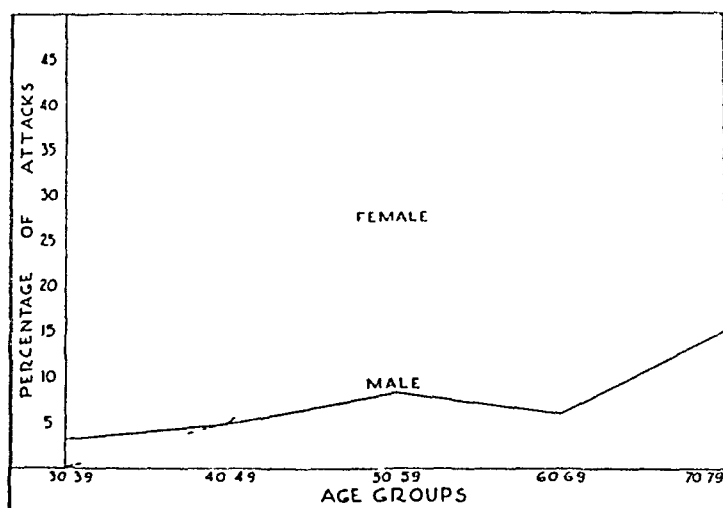


Chart 4—Diabetes in relation to age and sex

Hypertension—Hypertension is a common antecedent of coronary occlusion and was concluded by Levine^{3b} to be the most significant single etiologic factor, since it occurred in at least 40 per cent of his patients. Other authors have reported the incidence to be from 33 to 73 per cent¹⁴. Allen¹⁴ compared the incidence of hypertension in patients who had had coronary occlusion and in the general population and found it definitely higher in the former. In our series hypertension (as evidenced by a systolic pressure of 150 mm or more or a diastolic pressure of 90 mm or more) was present in 62.4 per cent of cases (table 2). It should be noted that many authors have considered hypertension to be present only when the systolic pressure was 160 mm or the diastolic pressure 100 mm; they have, therefore, obtained lower percentages than

14 Allen, W. The Relation of Arterial Hypertension to Angina Pectoris and Coronary Occlusion, *South Med & Surg* 96:377, 1934.

ours. However, since most patients with coronary occlusion are seen after the blood pressure has fallen, we believe that the figure of 62.4 per cent is lower than the actual incidence.

The frequency of hypertension rose directly with increasing age. From chart 5 it is seen that the incidence rose in a practically straight line from 28 per cent in men 25 to 34 years of age to 80 per cent in those aged 75 years and older. In females the incidence rose more rapidly from a similar figure of 25 per cent in those below 35 years to 90 to 100 per cent in those aged 45 years and older.

There was a definite difference between the sexes in the incidence of hypertension. Eighty per cent of the women in our series had hypertension, as compared with only 56.5 per cent of the men. Furthermore, hypertension or diabetes was present in 88.3 per cent of women and

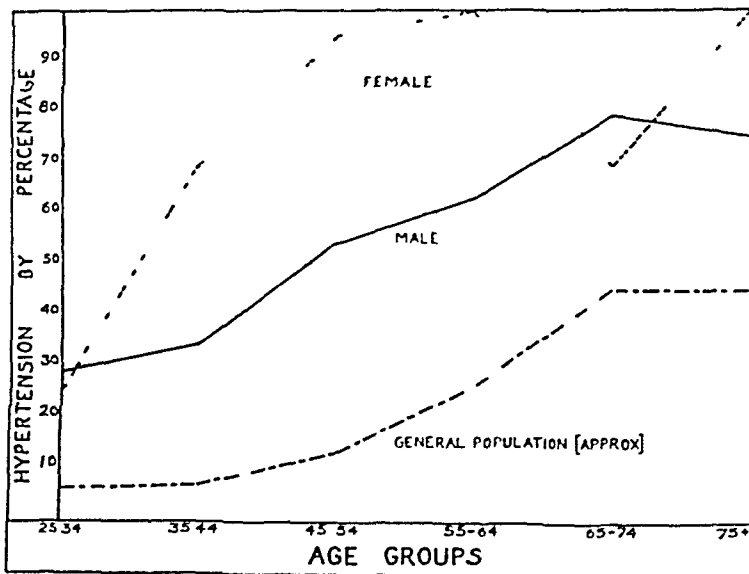


Chart 5—Hypertension in the various age groups in 500 cases of coronary occlusion as compared to hypertension in the general population

in only 59 per cent of men. It is thus seen that preceding hypertension or diabetes or both are present in the vast majority of women with coronary occlusion.

Hypertension did not affect the immediate prognosis, for the mortality rate was approximately the same for both hypertensive and non-hypertensive patients, in spite of a considerable increase in the incidence of heart failure and cardiac enlargement in the former. Conner and Holt¹ and Vander Veer and Brown² also found no relation between hypertension and the mortality rate.

Cardiac Enlargement—Closely related to the frequency of hypertension was that of cardiac enlargement, which was present in 59.8 per cent of cases. There was a direct correlation with age, for the incidence was only 35.9 per cent in patients below 40 but it rose

rapidly to a peak of 78.3 per cent in patients over 70 (table 2). Cardiac enlargement was more common in women than in men, occurring in 74 per cent of the former but in only 58 per cent of the latter, presumably because of the greater frequency of hypertension in women. Furthermore, women comprised 28 per cent of patients with enlarged hearts but only 14 per cent of those with normal-sized hearts.

The importance of cardiac enlargement lies in its close association with heart failure, which is the principal cause of death in cases of coronary occlusion and occurs almost always in the presence of an enlarged heart.¹⁵ Conversely, the favorable prognosis which we have found for young persons may well depend on the low incidence of cardiac enlargement in persons below 40 or 45 years of age. White and Bland^{3e} and Allen^{3f} also found a correlation between cardiac enlargement and the mortality rate.

Heart Failure—Congestive heart failure was closely associated with cardiac enlargement, occurring in moderate or severe degree in 50.8 per cent of our patients. When slight degrees of failure were included, the incidence was 69 per cent, rising progressively with increasing age from 30.8 in the fourth decade to 69.5 per cent in the eighth and was slightly higher in women than in men. As has been stated, it can probably be accounted for by the greater frequency of cardiac enlargement in women and in older patients.

An interesting finding was that pulmonary edema was more common in women than in men, the incidence being 20.5 and 14.5 per cent respectively. It is in these patients, particularly in women, that pain may be minimal during the attack, being masked by the pulmonary edema.

Shock—Symptoms of shock occurred in approximately one-half the patients and were equally common in men and women. The incidence was slightly greater in patients below 40 and in those aged 70 years or over, but this difference may not be significant, because the number of patients in these groups was relatively small. In view of the low mortality rate for young patients, the high incidence of shock in them suggests that shock alone is not of serious import as far as recovery is concerned but that heart failure, which is more common in older patients, is the dominant factor in the immediate prognosis.

Mode of Death—In a previous study¹⁵ it was shown that the most common cause of death in cases of coronary occlusion is congestive heart failure. It was the chief cause of death in 33 per cent of cases analyzed by us and in 16.5 per cent of additional cases it was associated

15 Master, A. M., Dack, S., and Jaffe, H. L. Coronary Thrombosis. An Investigation of Heart Failure and Other Factors in Its Course and Prognosis. *Am Heart J* 13: 330, 1937.

with severe shock. Death in one-half the cases therefore, was due to heart failure with or without shock. In patients below 50 years of age however, death from heart failure occurred in only 30.7 per cent of cases. This is to be expected (we have already drawn attention to the lower incidence of heart failure in the young). In patients under 50 the most common cause of death was arterial embolism, either peripheral or pulmonary. The incidence of this complication as the cause of death in such patients was 53 per cent, as compared with only 12 per cent in patients aged 50 years or more. Sudden death, too, was somewhat less common below 50. There were no differences in the cause of death between men and women.

COMMENT

Our findings, like those of other authors, indicate that persons of middle age and not of old age comprise the great majority of those suffering from acute coronary occlusion. In our series the condition was most common in patients aged 50 to 59 years, and it occurred almost as often in patients under 50 years as in those over 60. When the age at the initial attack was considered it was found that the peak was approached at the early age of 45 years. These figures, however do not indicate the true incidence of coronary occlusion in each age group, for this depends on the age distribution of the general population as well. The finding of fewer patients in our series between the ages of 60 to 64 years than between 50 and 54 years, therefore, may be due to the fact that there are fewer persons in the former age group in the general population, since there is a progressive decrease in population above the age of 45 years¹⁶. Therefore, in order to evaluate more accurately the influence of increasing age on the incidence of coronary occlusion, the number of cases in each ten year age group was correlated with the age distribution in the general population. This correlation was made for all patients as well as for men and women separately (chart 6). A figure was obtained for each age group which expressed the number of attacks of coronary occlusion per unit of general population in that age group. This figure is of value only when compared with the ratios for each age group. Since our series was collected in a hospital the patients of which are predominantly Jewish, we have taken as our basis the estimated Jewish population in New York city.¹⁷ In this group there is a progressive decrease in population above the age of 44.

16 Federal Census for New York City, April 1, 1930

17 Studies in the New York Jewish Population, New York, Bureau of Jewish Social Research, 1928, pp 14-18

It is seen in chart 6 that the number of attacks per unit of population rose progressively in each age group until the age of 74 years. Above this age there was an abrupt fall in the incidence of attacks, this has not been shown on the graph because of the small number of cases in our series in this age group. It is interesting, however, that in a recent survey¹⁸ of deaths from disease of the coronary arteries among insured persons there was a similar falling off after the age of 70 years. When the two sexes were compared it was found that the ratio of attacks in men per unit of male population rose more abruptly with age than did the ratio of attacks in women per unit of female population, particularly in the younger age groups. This again emphasizes the greater incidence of coronary occlusion in males than in females.

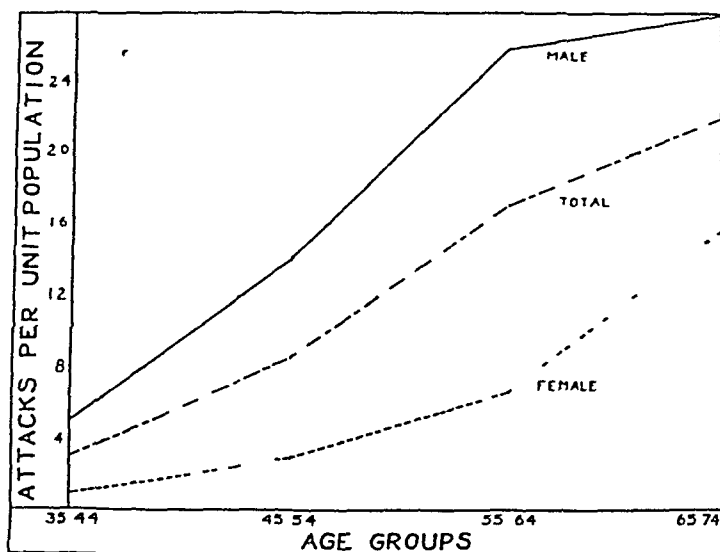


Chart 6—Ratio of attacks of coronary occlusion to the estimated Jewish population of New York city

While these observations suggest that the occurrence of coronary occlusion is associated with increase in age, a study of the influence of hypertension and a correlation of hypertension with age indicate that such a conclusion is not entirely warranted. We have pointed out (chart 5) that hypertension was present in only 28 per cent of men in our series below 35 years of age but that the incidence rose rapidly with age, reaching 80 per cent at the age of 70. In women hypertension was even more common, being present in 90 per cent of those over 44 years of age. Hypertension would seem, therefore, to be an important predisposing factor in coronary occlusion, particularly in the older age groups and in women. Before this conclusion is accepted, however, the incidence of hypertension in our series should be com-

18 Muhlberg, W., Medical Director, Union Central Insurance Company, Cincinnati, Ohio. Personal communication to the authors.

pared with that in the general population. Accurate figures for the latter, unfortunately, are practically impossible to obtain at present. Although there are a few reports¹⁹ comprising the cases of 42,000 persons, they give only an approximate incidence of hypertension in the various age groups. In addition, the number of persons in each group is relatively small. These studies show that the incidence of hypertension is approximately 5 per cent at the age of 25 and rises progressively to 26 per cent at the age of 55 and to 45 per cent above the age of 65 (chart 5). It is obvious that the incidence of hypertension in the 25 to 54 year group of males and females was about four or five times as high in our series as in the general population, in the 55 to 74 year group it was two or three times as high. This confirms the importance of hypertension as a precursor of coronary occlusion, particularly in young persons.

Of even greater significance in this connection are the conclusions regarding hypertension to be drawn from chart 7. It has been prepared in a similar manner to chart 6, that is, the male population in each age group has been broken down into hypertensive and nonhypertensive persons by applying the approximate percentages of hypertension derived for the general population. In each age group we calculated both the ratio of hypertensive men in our series to those in the general population and the ratio for those with normal blood pressure. Since the calculated percentages of hypertensive males in the general popula-

19 Thompson, R. J. C., and Todd, F. R. E. Old Age and Blood Pressure Problems, *J. Roy. Army Med. Corps* **40** 192, 1923. Alvarez, W. C., Wulzen, R., and Mahoney, L. J. Blood Pressures in Fifteen Thousand University Freshmen, *Arch. Int. Med.* **32** 17 (July) 1923. Weitz, W. Zur Aetologie der genuinen oder vascularen Hypertension, *Ztschr. f. klin. Med.* **96** 151, 1923. Dunham, G. C. Variation in Blood Pressure as Associated with Variation in Age and Body Weight, *Internat. Clin.* **3** 81, 1925. Diehl, H. S., and Sutherland, K. H. Systolic Blood Pressures in Young Men, Including a Special Study of Those with Hypertension, *Arch. Int. Med.* **36** 151 (Aug.) 1925. Life Conservation Studies. I. Physical Impairment Among Office Workers, II. Physical Impairment Among Industrial Workers, Cincinnati, The Heart Council of Greater Cincinnati, 1925. Richter, A. Ueber Blutdruck im hoheren Lebensalter, zugleich ein Beitrag zur Klinik des Hochdrucks, *Deutsches Arch. f. klin. Med.* **148** 111, 1925. Britten, R. H., and Thompson, L. R. Occupations. A Health Study of Ten Thousand Male Industrial Workers, *Public Health Bulletin* 162, United States Public Health Service, June 1926. Gelman, J. Hypertoniestudien. Alters- und Berufsverschiebungen im hamodynamischen System, *Ztschr. f. klin. Med.* **106** 310, 1927. Saller, K. Ueber die Altersveränderungen des Blutdrucks, *Ztschr. f. d. ges. exper. Med.* **58** 683, 1928. Riseman, J. E. F., and Weiss, S. The Age and Sex Incidence of Arterial Hypertension, *Am. Heart J.* **5** 172, 1929. Musser, J. H., and Phillips, A. W. Comparison of Blood Pressure, Blood Urea Nitrogen, Phenol-sulphonephthalein, and Urine Tests in the Aged, *J. Lab. & Clin. Med.* **15** 633, 1930. Davis, H. J. Notes on Blood Pressure in Old Age, *Human Biol.* **2** 264, 1930. Willius, F. A. Heart and Old Age. Study of Seven Hundred Patients Seventy-Five Years and Older, *Am. J. M. Sc.* **182**:1, 1931.

tion are only approximations, we applied a ± 10 per cent correction to each ratio obtained and plotted them as a band instead of a single line. The ratios for the age groups from 25 to 34 and from 75 to 84 were omitted because of the small number of cases.

It is seen that the ratio of hypertensive attacks to the hypertensive male population rises steeply with increasing age until 64 years and then falls slightly. The ratio doubles between the ages of 35 and 55. Although the incidence of coronary occlusion per unit of population is not so great in the nonhypertensive group, it, too, rises with age in about the same proportion as in the hypertensive group. Between the ages of 35 and 74 years coronary occlusion is from five to eight times as frequent in hypertensive as in nonhypertensive persons, but the

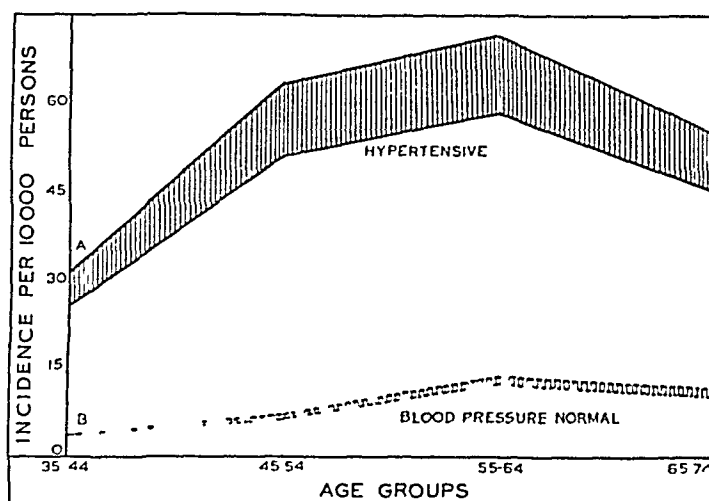


Chart 7—Ratio of attacks of coronary occlusion to the estimated Jewish population of New York city in relation to hypertension

incidence in both groups rises with age in about the same degree. Hypertension, therefore, plays the paramount role in the increasing incidence of coronary occlusion, but age alone also plays a part. Arteriosclerosis is the fundamental pathologic basis, but hypertension accelerates this process tremendously, particularly in the younger age groups.

These findings emphasize the importance of hypertension in coronary occlusion, but its exact role cannot be evaluated until more accurate figures on the incidence of hypertension in the general population are obtained. The arteriosclerotic process in the coronary arteries occurs spontaneously in some persons at a relatively early age but in the majority is preceded by hypertension.

That hypertension is not the only factor in coronary occlusion is evident. The majority of our patients under 45 were nonhypertensive. The blood pressure was also normal in cases of young persons cited by Durant^{8e1} and Franklin^{8f1}. Other predisposing factors have therefore been sought. Some authors have claimed that syphilis is common as

a cause of coronary occlusion in the young. This conclusion was not borne out in our series, for there were only 2 patients below 50 in whose cases the Wassermann reaction was positive, since both are living at the time of this report it is uncertain whether the closure was a result of syphilitic stenosis of a coronary ostium or of arteriosclerosis of the coronary arteries. Occlusion of a coronary artery has also been attributed to rheumatic fever, but rheumatic heart disease was present in only 1 of our young patients, and this was coincidental. It is also noteworthy that diabetes was uncommon in our young patients, whether male or female. Warren found that diabetic patients usually had coronary occlusion after the age of 50. We are tempted, therefore as several authors before us have done,²⁰ to invoke a familial tendency as an explanation of the occurrence of coronary sclerosis and occlusion in young persons. In our series, however, the incidence of heart disease in the immediate families of the young patients was found to be no greater than that in the families of the older ones.

The influence of hypertension on prognosis is not entirely clear. We have seen that for the young, with little hypertension, the prognosis was good and that for women, with more hypertension, the mortality rate was slightly higher than in men. However, the prognosis in the entire series was similar for the patients with and for those without hypertension, in spite of the higher incidence of cardiac enlargement and heart failure in men and women with hypertension. Conner and Holt,¹ too, found hypertension of no significance in the prognosis of an attack. It is evident that, while hypertension may predispose to coronary sclerosis and occlusion, the hypertensive patient progresses as well as the nonhypertensive patient after the occlusion has occurred. It is even possible that the increased blood pressure has a favorable influence on the coronary blood flow after occlusion.

Some investigators have held that the frequency of coronary occlusion at present is greater than formerly, particularly in the younger age groups. It seems more likely, however, that the increase is only apparent and is the result of greater accuracy in diagnosis and of greater interest in the disease. Knowledge of the frequency of coronary occlusion in young as well as in old persons is becoming widespread. Not only physicians but lay persons are more apt now to recognize mild or atypical attacks. Such a diagnosis as acute indigestion is no longer accepted without question. Furthermore the increasing use of the electrocardiograph brings to light instances in which the condition has been unsuspected or diagnosed as angina pectoris.

Nor is it necessary to postulate that disease of the coronary arteries and therefore occlusion appears at an earlier age today than formerly.

20 Musser, J. H., and Barton, J. C. The Familial Tendency of Coronary Disease. *Am Heart J* 7: 45, 1931. Levine²¹ Herapath and Perry.²² Glendy, Levine and White.²³

In a previous paper ²¹ we have shown that in the young the coronary vessels may be involved long before other arteries become sclerotic. In 9 cases in which arteriosclerosis was present only in the coronary arteries 8 of the patients were under 45 years of age. It would seem, therefore, that certain persons are susceptible to coronary sclerosis and occlusion and that this process often begins at a relatively early age and may remain localized to the coronary arteries. In the majority of young patients the retinal arteries were normal. In this connection our data concerning multiple attacks are pertinent. It was found that the incidence of first, second and third attacks was similar in each age group, that is, after an initial attack of coronary occlusion a man or woman 45 or 50 years old was as apt to have another attack as a person of 60 or 65. Apparently, once the sclerotic process is initiated its tempo is the same at all ages.

It is interesting to compare the course of coronary occlusion in the young and in the old. The outstanding difference is the much better prognosis for the former, even in the first attack the mortality rate rises with age. This relation, however, is not a direct one in all decades. It has been pointed out that the mortality rate rose gradually during the period from 45 to 59 years and then increased sharply, beginning at the age of 60. It is probable that after the fifties the degree of coronary sclerosis and myocardial involvement becomes definitely more advanced, so that a difference of even a few years about the age of 60 may be significant in prognosis. At first it may seem surprising that the prognosis is better for the young than for the old, for anastomoses are thought to manifest themselves only as a result of increasing disease of the coronary arteries and so appear in later years. It is apparent, therefore, that the outcome of the attack depends on other factors in addition to vascular anastomoses. Postmortem studies have indicated ²² that in the young the coronary disease may not be widespread but often may be localized to only one or two arteries, consequently, the heart muscle as a whole is in good condition and can withstand the occlusion of the diseased artery. Indeed, we have seen that for young persons the incidence of cardiac enlargement and heart failure is much lower than for the old, pointing to the reserve strength of the heart and accounting for the rarity of a fatal issue. Actually, death in the young is more often the result of a complication of the occlusion (particularly embolism) than of cardiac failure. Another point in favor of the survival of young persons is the lesser degree or total absence of arteriosclerosis outside the heart. The kidneys, brain and other organs often remain unaffected.

21 Master, A. M., Dack, S., and Jaffe, H. L. Coronary Artery Thrombosis. Mode of Death and Analysis of Fatal Cases, *New York State J. Med.* **37** 1707, 1937.

22 Leary ⁸⁸ Master, Dack and Jaffe ¹⁵

We have shown that the sexes exhibit several interesting differences in respect to coronary occlusion including incidence, age frequency of hypertension, frequency of diabetes and mortality rate. Formerly it was believed that coronary occlusion was rare in women, the ratio of men to women being given as 10:1 to 5:1. Recently it has been pointed out that women are more frequently affected in the proportion of 5:1 to 3:1. In our series the ratio was 3.4 to 1. The explanation of this change doubtless lies in the improved methods of diagnosis of and search for coronary occlusion, as we have discussed in a previous paragraph in the case of young persons. Unless one is on the alert for the presence of coronary occlusion in women one may miss the diagnosis entirely. It is probable that in the past coronary occlusion in women not infrequently has been labeled acute cholecystitis. In addition, it is our impression, based on insufficient data, that women are less apt than men to have severe, persistent pain and that the attack is more likely to begin with pulmonary edema, which may mask the pain. In such cases the diagnosis may be difficult to make. It may be mentioned that few women in our series smoked, and none immoderately. Tobacco, therefore, is not the cause of the apparent increase in coronary occlusion in women.

Many authors have found that coronary occlusion occurs at a later age in women than in men. Our experience confirms this observation. The greater susceptibility of older women to coronary occlusion may account for the rapid increase in the incidence of diabetes in women over 50, diabetes did not become more frequent with age in the males.

Another difference between the sexes was the higher incidence of hypertension in women. Only 1 of every 10 women with coronary occlusion failed to show either hypertension or diabetes; the ratio for women of 60 years and over was only 1 in 12. It is difficult to explain this difference, coronary sclerosis often occurs in men without diabetes or hypertension, but the foundation for this disease in women is laid by one of these factors. It is probable that when coronary occlusion occurs in women the sclerosis is more widespread and severe than in men, and as a result of hypertension the incidence of cardiac enlargement and heart failure is greater. This probably accounts for the higher mortality in women than in men (32 per cent as against 28 per cent). We have shown¹⁷ that the mortality rate is directly dependent on cardiac enlargement and heart failure.

SUMMARY

The influence of age, sex and hypertension on the incidence, clinical course and prognosis of coronary occlusion has been analyzed in 500 consecutive cases.

Approximately two thirds of the attacks occurred between the ages of 45 and 65 and almost one third before 50 years. The peak occurred in the sixth decade.

The number of initial attacks rose progressively until the age of 45, then a level was maintained until the age of 64, after which there was a rapid decrease. However, when the number of attacks was correlated with the census of the general population in each age group, there was a progressive rise in the incidence of attacks with advancing age to 74 years.

Particular attention was paid to a group of 39 patients aged 27 to 39 years. The susceptibility of these young persons to coronary sclerosis and occlusion could not be attributed to rheumatic fever, syphilis, diabetes, hypertension or a familial or hereditary trait.

The mortality rate varied with age, increasing gradually until the age of 59 and rising sharply in the older age groups. Coronary occlusion is rarely fatal below the age of 40, since the occlusive process is often localized to one artery and the myocardium is not diffusely damaged.

The frequency of multiple attacks was the same in all age groups. Young and old persons are equally susceptible to subsequent attacks of coronary occlusion after an initial attack.

The commonest cause of death before the age of 50 was arterial embolism, after 50 it was cardiac failure.

The ratio of men to women was only 3:4:1. The average age of the women was higher than that of the men, and the incidence in women below the age of 40 was relatively small.

Diabetes was frequent in women over 50 but uncommon in men below 70. In women the incidence rose sharply with increasing age.

Cardiac enlargement and heart failure increased with age, being uncommon in the young. They were more common in women than in men. Pulmonary edema with little or no pain not infrequently initiated an attack, particularly in women.

Hypertension occurred in more than half the men and in four fifths of the women. The incidence rose with age from 36 per cent in the fourth decade to 74 per cent in the seventh decade. There was no effect on the mortality rate.

Hypertension is an etiologic factor in coronary occlusion, for its incidence in our series was definitely greater than that calculated for the general population. Furthermore the ratio of attacks per unit of the hypertensive male population was five to eight times as great as that for patients with normal blood pressure although both ratios increased with age in the same proportion. Hypertension accelerates the aging process.

Mr Herbert Marks, assistant statistician of the Metropolitan Life Insurance Company, New York, assisted in the compilation of the data presented in this paper.

JUVENILE DIABETES MELLITUS

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LOS ANGELES

The purpose of this report is to review certain statistical findings on juvenile diabetes mellitus for comparison with other reports and to emphasize some of the features that become apparent from the study. The children studied have not all been continuously under our personal observation from the onset of diabetes many having had previous treatment elsewhere and others having moved to other locations and supervision. In most cases however, we have been able to follow their progress.

There were 341 children in this group, all the children with diabetes observed by us between April 1920 and January 1938 except 2 seen in 1917. In all of them diabetes developed before the sixteenth birthday, the earliest onset being at the age of 8 weeks and only 4 children being under 1 year of age when the disease was discovered. The children have been cared for in private practice, at the Children's Hospital since 1922 at the Cedars of Lebanon Hospital since 1930 and at the Los Angeles General Hospital since 1932.

The sex incidence in this series conforms on the whole to that noted by others, the patients being almost equally divided with a slight preponderance of girls (184) over boys (157). Thirty-seven children (10.8 per cent) of the entire group were Jewish and of the non-Jewish children 7 were Mexicans, 6 Negroes, 1 Italian, 1 Assyrian and 1 Portuguese. The sex distribution by age at onset is given in table 1.

The incidence of diabetes according to age at onset in this group does not correspond accurately with other reports. The highest peak for the entire group occurred at the 11 to 12 year period (chart 1) but there was another high peak at the age of 7 to 8 years. The peaks for girls occurred at 3 to 4 and 7 to 8 years with a constant high level at 9 to 10, 10 to 11 and 11 to 12 years, while for boys 7 to 8 and 11 to 12 were the outstanding ages. The sharp drop in incidence of onset during the fifteenth year seems to be universally observed.

HEREDITY

A positive family history of diabetes was obtained in 110 cases. In 216 there was no known diabetes, and in 15 it was unknown whether diabetes had existed in the antecedents. This represents a known incidence of 32.2 per cent. Of the Jewish group (37 children) the data are known for 36, 17 (46 per cent) of whom had a family history of diabetes. In the non-Jewish group the data are known in 304 instances, in 93 (30.6 per cent) of which there was a definite family history of diabetes. Of the children who had had diabetes for ten years or longer (in 4 instances the family history was unknown), 36.9 per cent were known to have a family history of diabetes.

There was a pair of twins who had diabetes. They were Jewish girls. In 1 of them diabetes developed at the age of 3 years 2 months, and in the other, at 3 years 11 months. They are both living at the time of writing, the duration of the disease being six years seven months and five years ten months respectively. Each of the 2 boys had a twin

TABLE 1—*Distribution by Age at Onset*

Age at Onset, Yr	Patients	Boys	Girls	Non Jewish	Jewish
0-5	92	43	49	86	6
6-10	126	54	72	110	16
11-15	123	60	63	108	15
Totals	341	157	184	304	37

brother, and 1 girl had a twin sister. These nondiabetic twins are kept under constant observation, but at the time of writing none have shown any signs of diabetes. The twins with diabetes had a family history of the condition and one of the other twins also had such a history.

PREVIOUS ILLNESSES

Illnesses prior to the onset of diabetes have been stressed as of etiologic importance. While acute illnesses, especially infections do lower carbohydrate tolerance and make existing diabetes more severe for only 24 per cent of this entire group did we obtain a history of an acute illness sufficiently close to the onset of recognizable symptoms to be considered a possible causative factor or precipitating event. On the whole, the records of preceding illnesses varied little from those obtained in the cases of other children of similar age.

Table 2 lists the conditions observed. The patients are classified according to age at onset to bring out the difference in frequency of certain conditions and infections at different ages. The table also indicates conditions occurring within one year of the onset of symptoms and conditions which seemingly precipitated the symptoms of diabetes.

Eighty-two patients (24 per cent) had conditions which were seemingly precipitating, and of these, infections were the factors in 58, or 70.7 per cent. Severe infections of the respiratory tract acting as precipitating factors accounted for 60 per cent of the 58 infections.

Tonsillectomy precipitated symptoms in 5 instances. Serum and vaccine reactions seemed to be the precipitating factors in 7 others, but we were probably told only of the reactions that were followed by symptoms, no mention being made of the many in which symptoms did not follow.

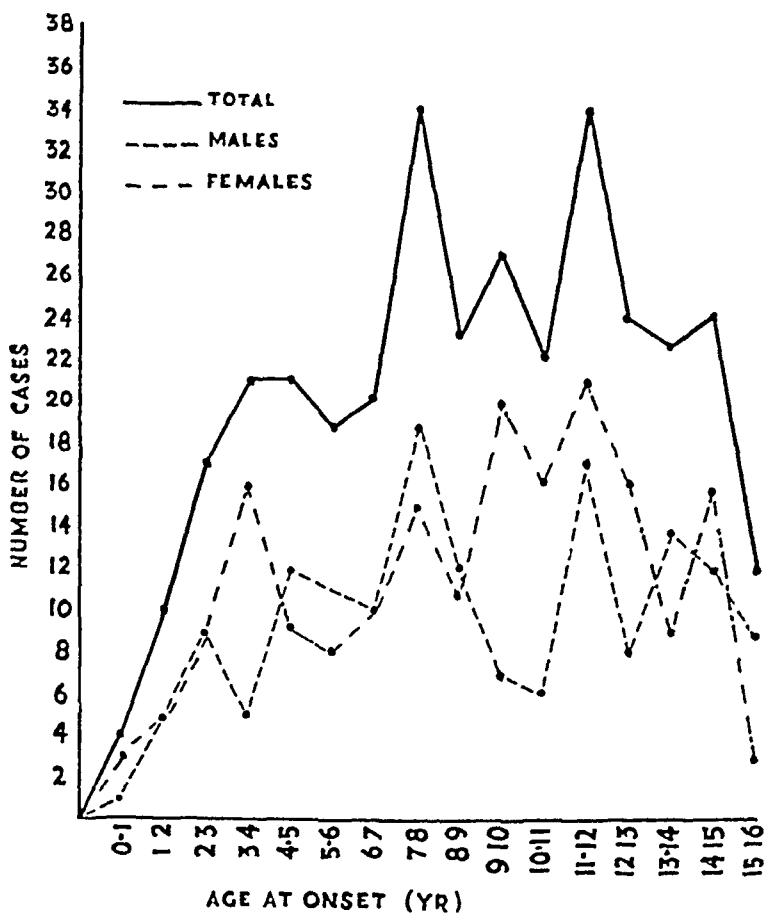


Chart 1—Incidence according to age at onset

SYMPTOMS AND DIAGNOSIS

The symptoms of diabetes in this group tended to follow the classic pattern. From 329 records in which the original symptoms were adequately described we found that polyuria occurred in 91.4 per cent of the cases, polydipsia in 89 per cent, loss of weight and strength in 79 per cent and polyphagia in 73.2 per cent. Table 3 shows these data and also indicates that there is little difference when the patients are divided as to age of onset.

TABLE 2—*Illnesses Before Onset of Diabetes*

History of	Age 0-5 yr			Age 6-10 yr			Age 11-15 yr		
	Total	Within 1 yr	Precipitating Symptoms of Diabetes	Total	Within 1 yr	Precipitating Symptoms of Diabetes	Total	Within 1 yr	Precipitating Symptoms of Diabetes
Measles	14	3	0	77	4	2	86	0	1
Mumps	3	0	0	25	2	0	34	0	1
Chickenpox	12	1	0	49	2	0	53	0	0
Infection of respiratory tract (severe)	41	0	10	48	0	16	41	0	8
Pertussis	21	3	1	62	0	1	51	0	0
Pneumonia	2	0	2	11	2	0	9	0	1
Smallpox	0	0	0	2	0	0	4	0	0
Scarlet fever	1	1	0	10	3	0	15	0	1
Diphtheria	0	0	0	4	1	0	4	0	0
Tonsillitis	15	2	3	25	2	3	19	0	1
Tonsillectomy	9	2	1	23	1	2	47	1	2
Obesity	6	0	0	5	0	0	11	0	0
Constipation	21	0	0	13	0	0	16	0	0
Appendicitis	1	1	0	3	1	0	1	0	0
Appendectomy	1	1	0	1	0	0	0	0	0
Allergy	5	0	0	6	0	0	4	0	0
Malnutrition	1	0	0	0	0	0	1	0	0
Rickets	1	0	0	1	0	0	0	0	0
Automobile accident	3	0	0	2	1	1	1	0	0
Abdominal pain and convulsions	1	0	0	0	0	0	0	0	0
Jaundice	1	0	0	0	0	0	1	0	0
Enteritis and colitis, acute	1	1	0	3	1	0	1	0	0
Torticollis	1	0	0	1	0	0	0	0	0
Papular rash (?)	1	0	1	0	0	0	0	0	0
Styes	1	0	0	0	0	0	1	0	0
Fracture of arm	3	0	0	3	0	0	2	0	0
Fracture of leg	1	0	0	0	0	0	1	0	0
Fracture of clavicle	1	0	0	0	0	0	0	0	0
Severe burn	1	0	0	0	0	0	1	0	0
Ichthyosis	1	0	0	1	0	0	0	0	0
Harelip and cleft palate	1	0	0	0	0	0	0	0	0
Acidosis and vomiting	2	0	0	3	0	0	0	0	0
Swallowed acid	1	0	0	0	0	0	0	0	0
Birthmark removed by cautery	1	0	0	0	0	0	0	0	0
Diarrhea	3	0	2	1	0	0	0	0	0
Hernia, inguinal	1	0	0	0	0	0	0	0	0
Hernia, umbilical	1	0	0	0	0	0	0	0	0
Fever (undetermined origin)	1	0	1	1	1	0	1	1	0
Sarcoid of Beck	1	0	1	0	0	0	0	0	0
Constipation with fever	1	0	1	0	0	0	0	0	0
Herniotomy				3	0	0	0	0	0
Mastoiditis (in 1 case associated with sinus thrombosis)				2	0	1	1	0	0
Mastoidectomy				2	0	1	1	0	0
Cretinism				1	0	0	0	0	0
Furunculosis				4	0	0	2	1	0
Cellulitis				1	0	1	0	0	0
Face							1	0	1
Wrist							1	0	1
Foot							1	0	0
Reaction to pertussis vaccine				1	0	1	0	0	0
Reaction to diphtheria antitoxin				1	0	1	0	0	0
Reaction to smallpox vaccination				2	0	2	1	0	1
Reaction to tetanus antitoxin				1	0	1	0	0	0
Serum sickness				1	0	1	0	0	0
Pyelitis				2	0	0	1	0	0
Damaged heart after diphtheria				1	0	0	0	0	0
Concussion				1	1	0	0	0	0
Undescended testis				1	0	0	0	0	0
Adenitis				1	0	0	3	0	0
Enlarged abdomen				1	0	1	0	0	0
Enlarged thymus				1	0	0	0	0	0
Eczema				1	0	0	0	0	0
Exophthalmic goiter				1	0	0	0	0	0
Thyroidectomy				1	0	1	0	0	0
Pinworms				1	0	0	0	0	0
Chorea				1	0	0	0	0	0
Tuberculosis of spine				1	0	0	0	0	0
Tuberculosis, pulmonary				1	0	0	3	0	0
Traumatic ulcer							2	0	1
Dengue fever							1	1	0
Injury to back							3	0	2
Injury to head							4	0	1
Bursitis							1	0	0
Renal colic with hematuria							1	0	0
Infection from vaccination							1	0	0
Operation for congenital hip disease							1	0	0
Quinsy with operation							1	0	0
Rheumatic fever							1	0	0
Gonorrheal vaginitis							1	0	0
Epilepsy							1	0	0
Abscess of ear							1	0	1
Heel torn off							1	0	0
Typhoid fever							1	0	0

We have analyzed the type of onset of symptoms only from the standpoint of whether it was acute or gradual. The onset was classified as acute if the symptoms developed to the point of being brought to attention on a given day or within about two weeks. If symptoms were noted later the onset was classified as gradual. The aforementioned 329 records are classified in table 4 as to age of onset.

Two hundred and sixty-five records included sufficient data to permit calculation of the number of days elapsing between the onset of symp-

TABLE 3—*Age at Onset of Symptoms*

Symptom	Entire Group	Onset 0-5 Yr	Onset 6-10 Yr	Onset 11-15 Yr
Polyuria	91.4%	90.9%	93.3%	90.0%
Polydipsia	89.0%	88.6%	90.9%	87.5%
Loss of weight	79.0%	75.0%	81.0%	80.8%
Polyphagia	73.2%	69.3%	75.2%	74.1%

TABLE 4—*Type of Onset*

Age at Onset, Years	Total Patients	Acute Onset	Gradual Onset
0-5	89	88.5%	11.5%
6-10	122	82.8%	17.2%
11-15	118	78.8%	21.2%

TABLE 5—*Age at Onset Correlated with Time Elapsing Before Sugar Was Found*

Age of Onset, Years	Average Number of Days Before Sugar Was Found
0-5	38
6-10	49.9
11-15	74.1

toms and the discovery of sugar. In spite of the typical nature of the symptoms and the acuteness of the onset, diagnosis was delayed for an average of fifty-four and five-tenths days for the entire group. The younger children group fared better than the older ones (table 5), obviously because the bathroom habits and general condition of the younger children were watched more closely. This was probably also true for the medical observation.

The unhappy significance of this delay in diagnosis is illustrated by the fact that among 274 patients on whom we had definite data as to the existence of acidosis when the diagnosis of diabetes was made,

approximately 4 of every 10 (37.2 per cent) had more or less severe ketosis, and 1 of every 5 (21.1 per cent) was in coma. Table 6 gives the distribution of ketosis and coma by age groups. Consideration of the data leaves much to be desired in the promptness with which the diagnosis is made and treatment instituted, particularly in the younger group, in which only 31.5 per cent demonstrated no acidosis at the time the diagnosis was made.

MORTALITY

The present status of 315 of these children is known. Fifty-five of them died (table 7). The remaining 26 were lost sight of. The total known mortality of the group was 16.1 per cent with a possible mortality of 23.7 per cent if all those unaccounted for are dead.

Insulin was first available to our patients in November 1922. Prior to this, diabetes had developed in 25, 16 of whom are known to be dead. Fourteen of the deaths occurred before the advent of insulin. Of this group not receiving insulin, 8 died within one month of the onset of

TABLE 6—*Age Incidence of Ketosis and Coma*

Age at Onset, Years	Total No of Patients	Ketosis, Percentage	Coma, Percentage	No Acidosis, Percentage
0-5	76	47.4	21.1	31.5
6-10	99	35.4	18.2	46.4
11-15	99	32.4	25.2	42.4

symptoms, 1 lived for seven years, 1 for six years, and 4 from two years and one month to two years and eight months. One hundred per cent, then, of those who did not receive insulin died, and 57 per cent of these died within the first month. The shortest duration of diabetes was five days, and the average was one year and seven months. Eleven, then, lived long enough to receive insulin. Of these, 8 are living, 1 is unaccounted for but was living when last heard from (one year previous to this study) and 2 are dead, each having lived five years and seven months after the onset of symptoms. Chart 2 represents the duration of diabetes in those not receiving insulin.

The number of known deaths of those who received insulin is 41. This represents a known mortality of 13.2 per cent of the total (301) that we have been able to follow. If those who have not been followed by us are all dead the maximum mortality increases to 20.5 per cent. The duration of diabetes in this group that have died varied from two days to fourteen years and seven months. This is shown graphically in chart 3, and attention is again called to the high mortality in the first month after diabetes developed.

TABLE 7—Analysis of Fifty-Five Deaths

Patient	Sex	Age at Onset		Year of Death	Duration of Diabetes		Cause of Death	Comment
		Yr	Mo		Yr	Mo		
Before Insulin								
1 LB	M	5		1917	2	6	Unknown	
2 BT	M	5	3	1921		—1	Coma	None first seen in coma
3 RN	M	6	1			—1	Coma	None, first seen in coma
4 AB	F	4	2	1922	2	2	Ketosis	Gangrene of nose
5 JM	M	1	6			—1	Coma	None first seen in coma
6 DS	M	2	11			—1	Coma	None, first seen in coma
7 HFB	M	9	4		2	1	Pneumonia	None
8 GY	F	9	6		7		Influenza	None
9 DS	M	7	1			—1	Coma	None, first seen in coma
10 LL	F	10			2	8	Coma	None
11 HH	M	7				—1	Coma	None, first seen in coma
12 LF	F	10				—1	Coma	None, first seen in coma
13 TG	M	7	9			—1	Coma	None first seen in coma
14 WC	M	12			6		Coma*	Infection of upper respiratory tract
After Insulin								
15 EB	M	3	1	1923	5	7	Myocardial failure	Sudden myocardial death following diphtheria with laryngeal obstruction
16 GV	F	8	11			—1	Coma	Pneumonia
17 AG	M	7			5	7	Pneumonia*	None
18 KE	F	3	1	1924		5	Coma	Severe enteritis
19 LJ	F	4	1			11	Unknown†	
20 AM	M	15		1925	1		Coma†	Stopped insulin operation done, diabetes not cared for
21 JP	F	3		1926	4		Unknown†	
22 BH	M	3	6		2	11	Diphtheria	None
23 WM	M	2	5			6	Pneumonia	Empyema
24 EW	M	4	5	1927		—1	Coma	Record indicates inadequate treatment
25 HH	F	2	6			—1	Hypoglycemia*	Overtreated
26 BC	F	11	6		2	2	Coma†	Appendectomy done no attention to the diabetes
27 GJ	F	4	1	1928	1	6	Coma*	Acidosis almost cleared when patient died suddenly no cause found at autopsy
28 WA	M	10	6			8	Coma†	Parents refused to allow diet and insulin
29 AMT	F	7	10			—1	Coma	Record indicates inadequate treatment
30 NJ	F	8	3			—1	Coma	Record indicates inadequate treatment
31 TC	M	11	1		1	2	Lymphosarcoma*	None
32 BA	M	9		1929	3	11	Coma	Lateral sinus thrombosis
33 JL	F	14			5	9	Influenza	Ketosis
34 AP	M	4	6	1930	4	2	Pertussis*	
35 RI	M	4				—1	Coma*	Otitis media
36 FC	F	8	2		8		Unknown†	
37 RF	F	11			5	6	Unknown†	
38 LW	F	6	9	1931	7		Cerebral embolus	Abscess of lung
39 RS	M	7	5		1		Coma*	Record indicates inadequate treatment
40 RR	M	5	10	1932	4		Coma*	Stopped insulin coma treatment delayed moribund on admission
41 BMeR	F	1	5			—1	Coma*	Pneumonia hyperpyrexia
42 FH	M	1	10			6	Coma	Stopped insulin coma treatment delayed died before any treatment was given
43 ES	M	11	4		1	6	Drowning	
44 MH	F	7	9	1933	5	8	Coma*	Hyperpyrexia
45 RB	M	1	6	1934	1	4	Thrombosis of lateral sinus	Flexner's dysentery acute nephritis
46 CJ	M	6	10			—1	Coma*	Gangrene of small intestine with peritonitis possibly due to large doses of castor oil before admission
47 JL	F		2	1935		—1	Acute pancreatitis*	Ketosis hyperpyrexia
48 MF	F	9			11	10	Coma*	Treatment delayed
49 PD	F	9	6		2	7	Coma*	Stopped insulin treatment delayed pneumonia herniation of cerebellum edema of lungs fatty liver hyperplasia thymus
50 RZ	M	9	9	1936	1	6	Pulmonary tuberculosis*†	Tuberculosis of spine
51 DS	F	7	8			—1	Pneumonia*	Pyelitis renal abscesses acute hepatitis fatty liver
52 JS	F	14	9		5	2	Coma†	Treatment delayed
53 RS	M	12	11		2	10	Head injury*	Cerebral thrombosis pulmonary embolism acute cystitis hepatomegaly
54 AJ	F	9		1937	14	1	Pneumococcal meningitis*	Pneumococcal pneumonia pneumococcal otitis media petrocitis
55 BJ	F	3			1	6	Coma*	Stopped insulin coma treatment delayed moribund on admission bronchopneumonia (terminal)

* Autopsy

† Did not die under our care

We have subdivided the fifteen years of our experience with insulin into three five year periods (table 8)

The steady improvement in the mortality rate and the duration of disease in the patients who have died was modified partly by the constant addition of new patients who had been exposed to the hazards of diabetes

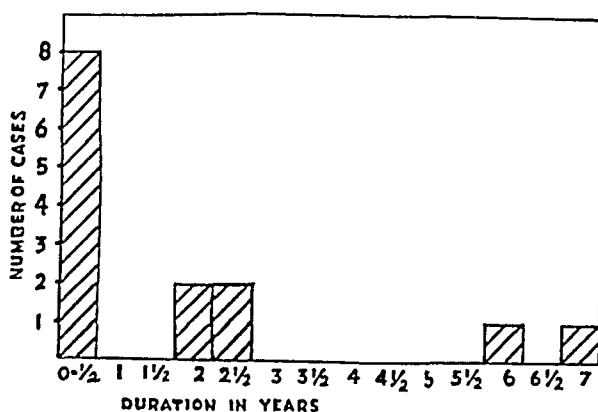


Chart 2—Duration of diabetes in 14 patients who died These patients received no insulin

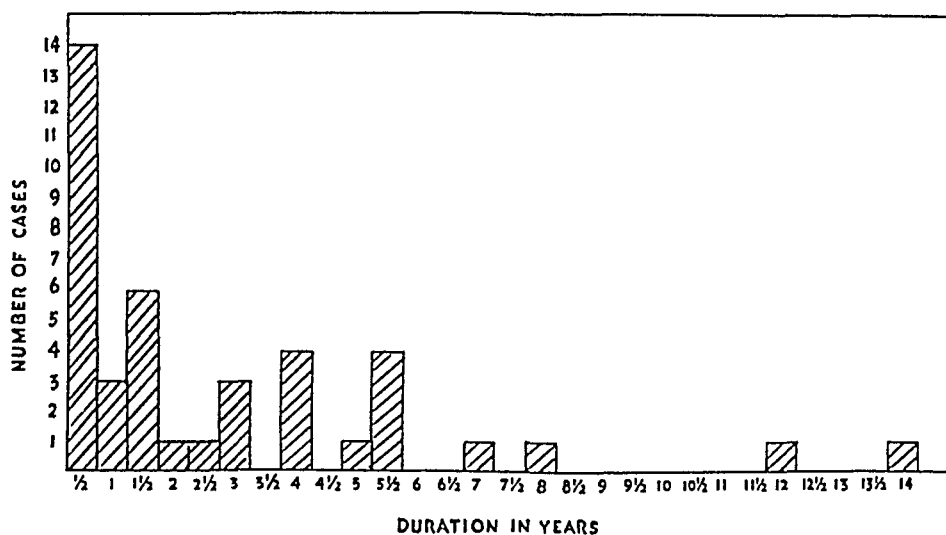


Chart 3—Duration of diabetes in 41 patients who died These patients were treated with insulin

for a shorter period, but we believe it also indicates earlier diagnosis and more adequate treatment

Of particular interest are 86 children in whom diabetes developed prior to January 1928 and for whom insulin was available, that is, those who had an opportunity to live ten years or more Twenty-one, or

approximately 25 per cent, have died, only 3 of the deaths have occurred since 1930. For those exposed less than ten years the mortality has been 92 per cent.

CAUSES OF DEATH

Inquiry into the causes of death in this entire group shows that 61.8 per cent of the deaths must be attributed directly to diabetes. The highest mortality was naturally in the group treated before insulin was available, in which 79 per cent died as a result of diabetes but we must admit that even in the period during which insulin was given there was no other adequate cause for 57 per cent of deaths. These figures are based on the total known causes of death, but the actual cause of death was unknown in 5 instances. In table 7 are listed the causes of death in both periods.

In the period before insulin was available, 10 of the deaths from diabetes were due to uncomplicated coma and 1 to severe acidosis with gangrene of the nose and malnutrition. In the period during which

TABLE 8—*Fifteen Years' Experience with Insulin*

Period	New Patients	Patients Held Over	Total	Total Known Deaths	Average Duration of Diabetes, Years
January 1923 to January 1928	67	11	78	12 (15.4%)	1.9
January 1928 to January 1933	126	66	192	17 (8.8%)	2.6
January 1933 to January 1938	123	175	298	12 (4.0%)	3.8

insulin was given 21, or approximately 50 per cent, died in coma. There was 1 death due to hypoglycemia and 1 to acute pancreatitis and ketosis. In 13 cases of diabetic coma there were no complications, but in 6 of these the insulin treatment was stopped or refused, and in 2 treatment was delayed until too late, in 1 case by the parents and in the other owing to delayed diagnosis. Four charts gave definite indication of inadequate treatment, and in 1 instance the treatment seemed adequate but sudden death ensued after the acidosis had cleared, the cause of which was not determined even at autopsy. In the other 8 cases of coma there was a severe complication, such as pneumonia in 3 instances, severe enteritis in 1, thrombosis of the lateral sinus in 1, otitis media in 1, hyperpyrexia in 1 and gangrene of the bowel with peritonitis in 1 (possibly the result of huge doses of castor oil administered by the parents before admission).

What we may call nondiabetic deaths during the period of administration of insulin include 3 due to pneumonia, 1 to myocardial failure after diphtheria, 1 to diphtheria, 1 to lymphosarcoma, 1 to influenza, 1 to pertussis, 1 to cerebral embolism, 1 to drowning, 1 to thrombosis

of the lateral sinus, 1 to pulmonary tuberculosis, 1 to injury to the head and 1 to pneumococcic meningitis. In all of these instances the diabetes was under satisfactory control at the time of death.

DURATION OF DIABETES IN THE LIVING

In the group of patients living at the time of writing (260) we eliminated all those in whose cases the disease was of less than six months' duration. The longest duration was seventeen years and seven months. The duration by years is presented in chart 4.

Two hundred and twenty-five (86.5 per cent) of these children have had diabetes for two years or over. This was about the average duration

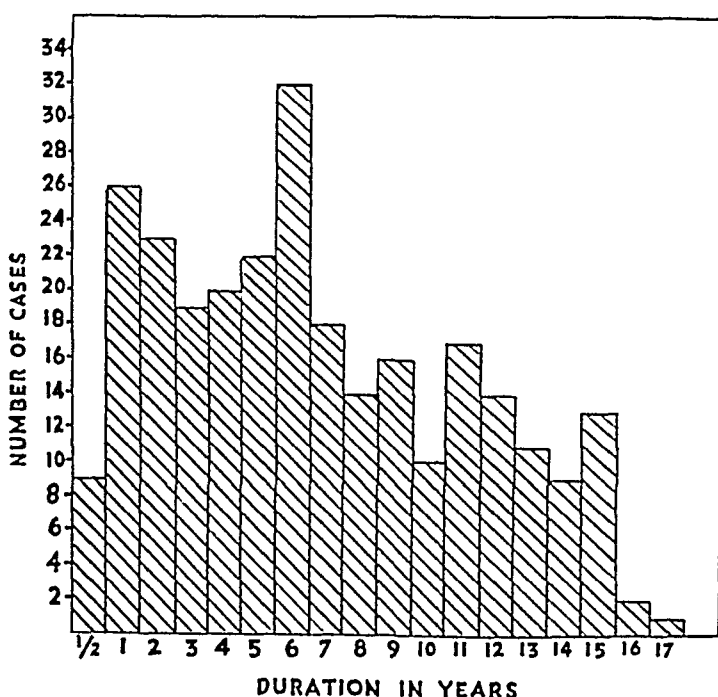


Chart 4—Duration of diabetes in 260 patients living at the time of this report

of life prior to the use of insulin. In table 9 we have listed the duration in years in relation to the total number in each year group. It is interesting to note that 62.7 per cent have a duration of five years or over, 25 per cent of ten years or over and 5.4 per cent of fifteen years or over.

NONFATAL COMPLICATIONS

There is perhaps no better way to evaluate the hardship of these diabetic youngsters and the efficiency of present day treatment than to consider the complications which have been successfully met during the course of the diabetes (table 10). Seventy-three children have survived

TABLE 9—*Duration of Diabetes*

Duration	No of Patients
6 months or over	260
1 year or over	251
2 years or over	225 (86.5%)
3 years or over	202
4 years or over	183
5 years or over	163 (62.7%)
6 years or over	141
7 years or over	109
8 years or over	91
9 years or over	79
10 years or over	65 (25%)
11 years or over	57
12 years or over	42
13 years or over	30
14 years or over	21
15 years or over	14 (5.4%)
16 years or over	3
17 years or over	1

TABLE 10—*Nonfatal Complications*

Complicating Factors	No of Cases	Complicating Factors	No of Cases
Ketosis	131	Tuberculous adenitis	1
Coma	73	Hilus tuberculosis (roentgen)	1
Measles	38	Adenitis	3
Mumps	14	Ichthyosis	1
Chickenpox	25	Parotitis (nonspecific)	1
Infection of upper respiratory tract	105	Anemia	1
Pertussis	19	Concussion	1
Pneumonia	7	Burns with skin grafting	2
Smallpox	0	Polomyelitis	1
Scarlet fever	4	Herniotomy	1
Diphtheria	3	Fracture of leg	2
Tonsillitis	46	Fracture of spine	1
Tonsillectomy	43	Pregnancy (18 pregnancies)	12
Obesity	48	Abortions	5
Constipation	4	Cesarean sections (7 operations)	6
Appendicitis	12	Gonorrheal vaginitis	1
Appendectomy	9	Conjunctivitis	1
Allergy	8	Paronychia	1
Gangrene of nose	3	Mastoiditis	1
Nutritional edema	1	Mastoidectomy	1
Enteritis (1 castor bean)	25	Edema (cause unknown)	2
Tracheotomy	1	Jaundice (catarrhal)	2
Furunculosis	15	Cystitis	2
Cellulitis	5	Pyelitis	3
Typhoid fever	1	Diphtheria carrier	4
Enlarged liver (no jaundice)	5	Pleurisy	1
Enlarged liver (jaundice)	1	Abscessed teeth	2
Cirrhosis of liver	1	Ovarian cyst, with removal	1
Needle removed	1	Tapeworm	1
Antrotomy	1	Retinitis	2
Hypoglycemia (1 with hemiplegia)	5	Cataracts	1
Periods of spontaneous hypoglycemia	1	Pilonidal cyst	1
Traumatic rupture of spleen	1	Pelvic inflammation with peritonitis	1
Operation for squint	1	Impetigo	1
Hypothyroidism	3	Renal abscesses	1
Vincent's angina	1	Cholecystitis	1
Dental caries	9	Roundworms	1
Food poisoning	1	Neuritis	1
Scabies	2	Hysterectomy	1
Pulmonary tuberculosis	1	Arteriosclerosis	1

coma, 33 on more than one occasion. One child was admitted to the hospital twenty-one times, in each instance the diagnosis of diabetic coma was made. (This patient is now married and has a daughter 3 years of age.) One hundred and thirty-one patients had ketosis of sufficient severity to require energetic treatment, 40 on more than one occasion.

Retinitis was observed in only 2 patients, both females. In 1 it developed during pregnancy. Cataract was observed only once. There was only 1 instance in which clinical evidence of arteriosclerosis was present. The incidence of tuberculosis was remarkably low.

Of all the complications the most interesting and probably the most significant was pregnancy. Prior to the period during which insulin was given girls having diabetes before the sixteenth year did not live long enough, as a rule, to marry. Sexual development was delayed and total amenorrhea was the rule rather than the exception.

TABLE 11—*Present Diets by Food Values*

Present Age	No. of Cases	Carbohydrate			Protein			Fat		
		Max. num.	Min. num.	Aver. age	Max. num.	Min. num.	Aver. age	Max. num.	Min. num.	Aver. age
0-3	4	150	150	140	60	50	55	110	60	82.5
4-6	8	170	120	134.5	60	50	57.4	90	70	81.2
7-9	26	220	135	147.2	85	60	65.5	120	60	93.6
10-12	41	220	130	165.7	90	60	70	140	70	93.7
13-15	31	250	125	175.4	100	65	76.9	125	70	104
16-18	45	290	120	173.1	100	60	74.5	170	75	98
19-21	13	210	150	160.7	105	65	75.4	120	75	83.3
22-24	15	250	170	169.3	95	60	75	170	60	96.3
25-27	3	180	140	166.6	50	60	72	90	80	83.3
28-30	3	160	60	123.3	70	60	63.3	120	65	91.7

A new generation has been added to medical history. These girls are beginning to marry and have children. In this group there were eighteen pregnancies in 12 women. Seven cesarean sections were performed on 6 women. There were five abortions, one of which was induced because of intractable ketosis and vomiting before the patient came under our care. In another case hysterectomy was done at the time of the abortion. The other abortions were spontaneous. One child died at birth. There was no maternal mortality.

DIETS

In planning diets we have not been particularly concerned about any definite ratios between carbohydrate and fat or between the total available dextrose and fatty acids. Our attention has been given primarily to adequate nutrition and growth for each patient. This obviously implies adequate protein, vitamins and minerals as well as adequate calories.

We believe that the improvement noted among children with diabetes during the past decade can be attributed almost entirely to more nearly

normal nutrition rather than to any particular dietary scheme. As the amount of carbohydrate allowed tends to exceed approximately 100 Gm a day the content of accessory factors automatically tends toward optimal values. Also, as carbohydrate is increased fat is automatically decreased if the caloric value of the diet is maintained at the same level.

Table 11 gives the food values of the diets with the averages for each in the various groups based on present age grouped by three year periods.

INTELLIGENCE TESTS

Intelligence ratings have been made of 62 unselected children in this group. At the time of the first test the average intelligence quotient was 105.4, standard deviation 11.7 ± 0.89 . The intelligence quotients of the children in this group were well in advance of the normal distribution for unselected children as indicated by intelligence quotients above 110 (42.1 per cent), from 90 to 110 inclusive (47.4 per cent) and below 90 (10.5 per cent). Terman's normals for unselected children are as follows: above 110, 20.6 per cent, 91 to 110, 60 per cent, and below 90, 19.4 per cent.

SUMMARY

The statistical data in 341 cases of juvenile diabetes are presented. No new theories or principles have been developed in the course of the study. The purpose has been to add to the accumulating data on the various phases of juvenile diabetes.

HYPERTHERMIA, GENUINE AND SPURIOUS

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Richet,¹ in his monograph on animal heat, tabulated 109 examples of hyperthermia in man with temperatures ranging from 42 to 44.6 C (107.6 to 112.2 F). There were 13 survivals in this group. He rejected as unreliable several reported observations of temperatures from 44.1 to 50 C with recovery and expressed unwillingness to accept as valid any observation of temperature above 46 C (114.8 F). This decision was based not merely on clinical studies but on extensive physiologic experimentation and observations on various mammals. Hombourger² defined fever as a morbid state resulting from exaggeration of proteolysis and disturbance of the heat-regulating mechanism, and he designated as hyperthermia a high elevation of temperature, whatever the cause. A fever with a temperature above 41 C (105.8 F) he designated as "hyperthermic fever." This author expressed agreement with Richet. He mentioned the famous cases of Jacobi and of Heber Jones, as well as the patient of Du Castel³ who by tapping the upper end of the thermometer succeeded in registering a temperature above 160 C (320 F). He added the caustic remark that in France one exercises reserve in reporting cases of this sort contrary to the custom in certain countries. He tabulated 33 cases of hyperthermia reported in the literature since Richet and added 1 new case of his own, in which the maximum temperature was 44.2 C (111.6 F), with recovery.

The clinical reports of hyperthermia may be grouped into different classes: (1) instances of proved trickery in which the thermometer has been caused to register a high temperature by artificial means not related to body heat, (2) instances of suspected trickery not clearly proved, (3) hysterical fever, (4) hyperthermia originating in disturbance of the central nervous system, (5) hyperthermia of heat stroke, (6) therapeutic hyperthermia, (7) fever of disordered metabolism and intoxications, (8) fever of infectious disease and (9) hyperthermia of complex causation.

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1 Richet, C. *La chaleur animale*, Paris, Felix Alcan, 1889.

2 Hombourger, P. *Les fièvres hyperthermiques*, Thesis, Paris, no 126, 1919.

3 Du Castel. *Simulation thermique chez une hystérique*, Bull et mem Soc med d hop de Paris 1 174 (April 25) 1884.

Hyperthermia of Trickery—Some of the classic examples of fraudulent hyperthermia are worthy of brief mention. Early in 1880, Little⁴ observed a woman aged 23 years in the Adelaide Hospital, Dublin, Ireland, who had fallen on the back of her head some days before. On April 19 her axillary temperature registered 115 F, and the same reading was obtained at 5 a m on April 20. A few hours later the Fahrenheit thermometer registered 99.4. On Monday, April 26, a temperature of 125.5 F was recorded, and later the temperature was 127 F on two occasions. Subsequently it reached 130.8 F. Late in May the patient appeared to be convalescent. Mackenzie,⁵ in a letter to the medical publication in which the case had been reported, suggested to Little that he take the temperature always with two or more thermometers simultaneously. Mackenzie⁶ himself was at that time observing a woman at the London Hospital, whose case was later reported to the Clinical Society. This patient was admitted Feb. 25, 1879, with a painful stump after amputation at the thigh in 1878. The temperature registered 108 and 111 F on different occasions. After surgical revision of the stump she was discharged in August. She was readmitted on October 21, and another piece of bone was removed from the amputation stump. In January 1880 there were numerous recordings of temperatures between 108 and 114 F and records of a temperature of 114.2 F on January 16, 120.8 F on January 22, 116.6 F on January 23 and 116.8 F on January 26. The patient was readmitted on August 16, and the thermometer again registered high temperatures. Simultaneous records with two or more thermometers were inconsistent, two instruments in the same axilla registered 105.5 and 101 F respectively, and simultaneously with an oral and rectal temperature of 98.6 F the axillary temperature was 104.6 F. Later the patient confessed that she had applied poultices and hot water bottles to the thermometers. Mahomed,⁷ in the discussion of this case, reported a similar one, in which the patient was able to produce all sorts of variations in the readings, from normal to 120 F. At one time simultaneous records with three instruments gave readings of 107 F in the mouth, 102 F in one axilla and 114 F in the other axilla. Once a reading of 128 F was recorded. The patient's technical method was never discovered. Newnham⁸ who

4 Little, J. Case of Hyperpyrexia in Adelaide Hospital, Dublin, *M. Times & Gaz.* **1** 457 (April 24), 482 (May 1), 510 (May 8), 585 (May 29) 1880.

5 Mackenzie, S. Abnormally High Temperatures, *M. Times & Gaz.* **1** 620 (June 5) 1880.

6 Mackenzie, S. A Case of Excessively High Temperatures, *Lancet* **2** 796 (Nov. 5) 1881.

7 Mahomed, F. A. A Case of Excessively High Temperatures, *Lancet* **2** 796 (Nov. 5) 1881.

8 Newnham, W. H. C. Hyperpyrexia, *Lancet* **2** 894 (Nov. 19) 1881.

served as medical ward clerk and observed the patient closely from Dec 1, 1879 to Feb 28, 1880, was at first skeptical but was eventually convinced that the high temperatures of this patient were genuine. With his fingers in the axilla and without the slightest friction against the thermometer he observed temperatures of 109 and 111 F. The skin felt burning hot. It seems, therefore, that this patient may have had genuine as well as fraudulent hyperthermia.

Galbraith,⁹ in 1891, reported the "Omaha case." The patient was a married woman aged 26. She was thought to have an abdominal pregnancy. Many fragments of bone (over 1,000) were removed from her vagina and rectum from time to time, which later were found to be bones of birds and mammals (chicken, mutton or beef bones). Temperatures of 112, 96, 107, 125, 145, 117, 145 and 98 F were recorded. At one time a temperature of 112 F was recorded simultaneously by two thermometers, one beneath the tongue and one in the axilla, but it seems that 112 F was the uppermost limit of the columns. With special thermometers simultaneous readings at one time were 145 F in the axilla and 125 F beneath the tongue. Half an hour later the temperature was 98 F. With every precaution to detect fraud, with the patient nude and sitting in a chair, simultaneous observations of the temperature in the axilla and under the tongue were 137 and 131 F respectively. On another occasion the axillary temperature was recorded as 131 F while the temperature simultaneously registered in the popliteal space was below normal. The highest temperature observed by the physician was 151 F but the hospital nurse made one record of 171 F. The fraudulent character of this patient was later exposed by Summers¹⁰ and Poe¹¹ but they were not able to elucidate the technic by which the remarkable thermometric records had been produced. Apparently hot water was sometimes employed but this could hardly explain the observations of Galbraith.

Jones,¹² in 1891, reported the case of a girl aged 14 whose temperature on various occasions had been recorded as 108, 109, 114, 97, 114, 115, 115, 135, 150, 156 and 99.5 F. When this patient was seen by Holder, she was able to produce apparent axillary temperatures of 98, 103, 114.4 and 97 F within a few minutes. The girl was an athlete and a contortionist, but her technic for causing high thermometric

9 Galbraith, W. J. A Remarkable Case, *J. A. M. A.* **16** 407 (March 21) 1891.

10 Summers, J. E. Omaha's "Remarkable Case" of High Temperature. An Undoubted Hysterical Fake, *Omaha Clin.* **4** 115 (Sept.) 1891.

11 Poe, C. T. A Chronic Malingerer, *Omaha Clin.* **4** 269 (Feb.) 1892.

12 Jones, H. A Case of Wonderful Temperature, *Memphis M. Month.* **11** 252 (June) 1891, High Temperature, 150° F, *ibid.* **11** 445 (Oct.) 1891.

readings has not been explained. Jones considered her to be free from guile and trustworthy in every respect.

Jacobi,¹³ in 1895, presented before a distinguished audience his report of a man aged 29 observed at the German Hospital, New York, in January 1893. The temperatures of this patient had been recorded as 111, 112, 113.4, 117, 118, 123, 135, 131, 136, 133, 124, 148, 136, 137, 148, 135, 132, 135, 142, 148, 115.8, 113, 109.8, 143.8, 142, 125 and 132 F. A few days later (March 13) he stole away from the hospital. In the discussion of this case, William H. Welch expressed himself as completely skeptical of the trustworthiness of the observations, George Dock asked about the temperature of the freshly voided urine (which had not been tested), William Osler asked about the heat of the abdominal skin. Jacobi, however, insisted that his observations represented facts.

With all due respect for the skill and integrity of the observers, one must share the total skepticism of Welch in regard to the validity of these recorded observations of the temperature of the human body. One must therefore consign these examples to the first two of the aforementioned classes of hyperthermia, namely, instances of proved trickery or of suspected trickery not clearly proved, in which the high thermometric readings are evidently not related to body heat.

The technical methods by which false high thermometric readings (fever of the thermometer) may be produced have not been fully elucidated. When the patient has access to a hot water bottle, a steam pipe near the bed or some other source of external heat, this would seem to offer the simplest means of forcing up the column in the thermometer. No especial skill is required to accomplish this result. Another trick depends on friction. If one holds the thermometer shaft parallel to the index finger with the bulb firmly pressed into the ball of the finger and then rubs this bulb and the adjacent finger tissue vigorously with firm pressure on a taut piece of cloth, one will quickly sense the increased temperature in the finger, and the column in the thermometer may be caused to record a high temperature. This can be accomplished with one hand. Another technic, requiring slightly more skill and practice, consists in holding the thermometer with the bulb tightly pressed between the thumb and the forefinger while the forefinger is vigorously rubbed up and down on the thumb and on the compressed thermometer bulb. Another procedure depends not on heating the thermometer but on displacement of the column of mercury by mechanical jarring. By vigorously snapping the upper end of the thermometer with the finger or thumb so as to drive the glass toward the bulb, one may displace the column of mercury toward the top of

¹³ Jacobi, A. Hyperthermy in a Man up to 148° F (64.4° C), *Tr. A. Am. Physicians* 10:158 (May) 1895.

the instrument The mercury column may become separated (broken column) so that there are vacant spaces in it along the shaft, but when one has developed sufficient skill it is possible to get the mercury up to a high level without a break in the column Such tapping may be accomplished with one hand if the bulb of the instrument is held in the mouth, the axilla the rectum or the vagina The procedure requires some technical skill, and a noise is produced by the tapping which may be heard by a patient in the neighboring bed The height of the reading attainable by this method is limited only by the length of the capillary of the instrument One may also displace the mercury upward by swinging the thermometer in a narrow arc with the bulb nearer the center of rotation a manipulation just the reverse of that used to throw down the mercury column before use This trick nearly always produces a broken column of mercury With experimentation and practice I have become reasonably adept in these technical procedures

Other fraudulent tricks are suggested in the literature on hyperthermia Mahomed stated that one may produce a high reading by wrapping the thermometer bulb in silk, inserting it in the mouth, inhaling through the nose and then exhaling through the mouth I have not been able to confirm this It has been suggested also that muscular movement may produce heat of friction in the axilla so as to cause a fraudulent high reading and that one may rub the thermometer bulb with the tongue or produce friction by rapidly repeated contraction of the sphincter muscles so as to give rise to fraudulent high readings for oral or rectal temperatures I have entirely failed to confirm these suggestions even after the expenditure of considerable effort Of course a special technical skill may be involved which I have failed to master

In order to avoid deception by these or other tricks the physician may have recourse to multiple simultaneous observations of the temperature One or more thermometers may be placed in each axilla, another beneath the tongue and another in the rectum the stem of each instrument being held steadily by the hand of an observer and never entrusted to the patient Reasonable agreement of the readings would indicate reliability, while a marked variation shown by one or more of the thermometers would point to error or fraud The temperature of the freshly voided urine and feces should also be observed

Hysterical Fever—The recognition of hysterical fever and hyperthermia originating in disturbance of the central nervous system is justified in part by animal experimentation Richet by passing a needle into the brain of the rabbit was able to cause a rise in temperature from 39.2 C (102.6 F) to 42.5 C (108.5 F) without other recognizable alterations in behavior of the animal He was unable to

recognize a localized "heat center," however, and even today there is no certain agreement in regard to the exact portions of the brain concerned with this phenomenon. Examples which may be tentatively assigned to these categories are not wanting in the literature.

Crouzet¹⁴ accepted hysterical fever as a definite entity, distinct from the hyperthermia of trickery, or fever of the thermometer. He reviewed in considerable detail numerous examples of this condition described in the literature previous to 1895. Nearly all of the patients were women with other manifestations of hysteria. The temperature curves were extremely variable, and as a rule the physical well-being of the patient was remarkably good considering the temperatures recorded. Crouzet attempted to classify the conditions under such headings as (1) hysterical fever proper and (2) hysterical fever with visceral pseudodisease, that is, pseudotyphoid, pseudomeningitis, pseudo disease of the lung, pseudoperitonitis or pseudomalaria. However, he considered such a classification premature.

The manifestations of hysteria present difficulties in differential diagnosis, and it seems probable that cases of the hyperthermia of trickery and hyperthermia associated with genuine gross organic disease of the central nervous system have been reported from time to time as examples of hysterical fever. The lines dividing the three classes of hyperthermia may therefore be considered as not sharply defined.

Soulier¹⁵ has recorded an example of hyperthermia apparently best designated as hysterical fever. The patient, a delicate woman, after a serious disappointment on Sunday morning fell into a narcoleptic state. She was absolutely insensible. The following night her temperature (axillary and vaginal) reached 44 C (111.2 F). On Monday and on Tuesday the temperature reached the same level. The patient recovered on the fifth day without memory of the events preceding the trance. The profound slumber resembled chloroform narcosis. Deception seems to have been reliably excluded in this case.

A more recent example of hysteria or of trickery has been recorded by Lhermitte and Aman-Jean,¹⁶ and it illustrates the difficulty of distinguishing the two. The patient, a woman aged 44, received several applications of radium to a carcinomatous uterine cervix. On May 23 (1936) she had severe chills and violent hallucinations, and the temperature of 43 C (109.4 F) was recorded by three thermometers. For seven days the rectal temperature was between 40 and 43 C (104

14 Crouzet, M. *La fièvre hystérique*, Thesis, Paris, no. 10, Paris, G. Steinheil, 1895.

15 Soulier, H. *Hyperthermie apyrétique correlative avec état narcoleptique*, *Lyon méd.* **93**: 5 (Jan. 7) 1900.

16 Lhermitte, J., and Aman-Jean, F. *Hyperthermie et pithiatisme. La fièvre du thermomètre*, *Rev. neurol.* **67**: 206 (Feb.) 1937.

and 109.4 F) At 7 a m on May 30 she was given a capsule of methylthionine chloride (methylene blue) and was told that if her urine became blue she would experience a severe chill and would then recover At 10 p m there was a violent chill, the urine was blue, and the temperature at 6 a m on May 31 was normal There was no more fever, and the patient was discharged June 6 Great care was exercised to prevent fraud While the thermometer was in the rectum there was no movement of the thighs, nevertheless, the authors concluded that the temperatures were fraudulent and recognized that some persons possess extraordinary talents (out of all proportion to their mediocre or inferior intelligence) for trickery which even the most scrupulous observers may not detect The hyperthermia in this case might be considered by some as hysterical fever

Hyperthermia Referable to the Central Nervous System—Hyperthermia in association with severe trauma or infectious lesions of the brain or of the upper part of the cervical portion of the spinal cord has been repeatedly observed In many instances there can be no ground for suspicion of fraud because of the desperate condition of the patient who may even be in coma Brodie,¹⁷ in 1837 seems to have reported the first example the case of a man with a fatal fracture of the cervical portion of the spine, with a temperature of 43.9 C (111 F) Macgregor¹⁸ observed a man aged 76 in terminal coma apparently due to cerebral hemorrhage with an axillary temperature of 109 F three hours before death Massey and Carter¹⁹ recorded terminal hyperthermia in a man aged 27, in whom an abscess of the brain developed two days after mastoidectomy with an axillary temperature of 108.6 F shortly before death Macewen²⁰ reported the case of a youth aged 19 with a cerebellar abscess who showed a temperature range from 104 to 108 F on the day of his death Many similar examples have been reported

Hyperthermia of Heat Stroke—Hyperthermia of heat stroke or sunstroke not uncommonly reaches a temperature of 110 F or above Osler stated on the authority of F A Packard that 31 patients with sunstroke were admitted to the Pennsylvania Hospital in the summer of 1887 and the temperature of the majority was between 110 and

17 Brodie, B, cited by Hambourger²

18 Macgregor, D A Case of Hyperpyrexia with Coma, *Brit M J* 1 1199 (May 16) 1896

19 Massey, A, and Carter, H S Terminal Hyperpyrexia, *Brit M J* 2 922 (Nov 11) 1922

20 Macewen, W Pyogenic Infective Diseases of the Brain and Spinal Cord, Meningitis, Abscess of Brain, Infective Sinus Thrombosis, Glasgow, James Maclehose & Sons, 1893

111 F Muscular activity without adequate dispersion of heat from the body would seem to be important in this condition

Therapeutic Hyperthermia—Therapeutic hyperthermia represents a relatively recent development It may be induced by infection (malaria), by intoxication (typhoid vaccine), by bactericidal or bacteriostatic chemicals, by bacteriophage, by application of external heat or by use of other forms of radiant energy Because of the practical application of these measures in the treatment of disease conditions, a rather voluminous literature relating to them has already accumulated, and active investigations are in progress A review of these artificially induced fevers would lead beyond the scope of the present paper

Fever of Disordered Metabolism and Intoxications—Of the metabolic fevers, perhaps the best known is that associated with exophthalmic goiter, in which disease there is a definitely demonstrable overproduction of body heat as the result of excessive oxidation However, the temperature in this disease does not ordinarily approach the level of hyperthermia Drug intoxications may be associated with elevated temperature In strychnine poisoning the muscular spasms lead to increased heat production Other poisons, such as aconitine, colchicine, digitaline and especially veratrine, have been found to induce high temperatures (45.6 C, or 114 F) in dogs Richet and (later) Hombouger have reported experimental observations in this category

Fever of Infectious Disease—Elevation of body temperature associated with active infection is so common that the casual observer often considers one the necessary companion of the other, and some would maintain that elevation of temperature in infection constitutes the only genuine fever, all other examples of increased temperature being placed by them in other categories Very high temperatures have been observed, especially in cases of scarlet fever, rheumatic fever, pneumonia, malaria, tetanus, typhoid fever, abscess of the liver, meningitis, puerperal sepsis and other bacteremias When, however, the temperature reaches the level of hyperthermia (41°C or 105.8 F) one is inclined to consider the infectious fever as dangerous to life itself Probably physicians have been accustomed in the past to ascribe too great importance to high temperature when, in fact, the danger is due to other disturbances of which the temperature is merely one manifestation

Hyperthermia of Complex Causation—Under this caption should be mentioned examples of infectious fever in which further increase of temperature is induced by therapeutic measures, such as the use of typhoid vaccine for chorea, external heat for rheumatic fever and injection of mercurochrome and therapeutic serum or bacteriophage for septic conditions (Hugh Young reaction) One also includes examples

in which the patient, having had a fever due to infection, finds it convenient and profitable to perpetuate the kindly care by production of fraudulent high temperature readings. One easily visualizes the successive stages of this condition, which may eventually be terminated by detection of fraud.

SUMMARY

1 Temperatures above 46 C (114.8 F) in man should generally be considered the result of fraud or trickery and are not to be accepted without more convincing proof than has, so far, been presented in any instance.

2 Temperature readings between 41 C (105.8 F) and 46 C (114.8 F) properly designated as hyperthermia, should be accepted as valid only after the most careful scrutiny of the evidence in each case.

3 Some of the technical tricks for producing false temperature readings have been exposed and safeguards against deception indicated.

4 Apparently there is a genuine hyperthermia of hysterical origin, and certainly there is hyperthermia due to lesions of the central nervous system, to heat stroke, to intentional application of excessive external heat and other therapeutic thermic procedures, to intoxications and to infectious diseases.

PROLONGED HYPERTHERMIA

REPORT OF A CASE WITH NECROPSY

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AND

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Examples of temperatures of 45 C (113 F) in man are sufficiently uncommon to deserve careful study and report, and examples of temperatures above 40 C (104 F) persisting for several weeks at this level are also unusual. At times, patients with such temperatures have been made the subjects of undesirable publicity. They present problems which are not yet completely elucidated. Osler,¹ in 1909, said

It is a suggestive fact that the cases of paradoxical temperatures reported of late years, in which the thermometer has registered 112° to 120° or more, have been in women. Fraud has been practised in some of these, but others have to be accepted, though their explanation is impossible under our known laws.

This statement still holds true in 1939. For these reasons the following case report is presented in considerable detail.

REPORT OF CASE

S V, a white woman, was born in the United States on Dec 24, 1911. Her father was killed in the World War. Her mother, two brothers and one sister were living and well. She had had measles and chickenpox. Otherwise she had been well until 1934, when, during her training as a student nurse, she had an attack of cholecystitis treated by cholecystectomy. Later, while employed as a graduate nurse in a hospital in Philadelphia, she had an infection in her left index finger, apparently due to a hemolytic streptococcus. She was treated at the Infirmary of the Philadelphia Hospital for Contagious Diseases on March 8, 1936 and subsequently. The finger was incised several times, and the distal phalanx was amputated. For a long time afterward the patient continued to have a temperature between 100 and 102 F for which there was no evident cause. Later there developed abdominal pain, and she was sent to the Philadelphia General Hospital for study. There the finger was curetted, but it failed to heal, and on

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1 Osler, W, and McCrae, T. The Principles and Practice of Medicine, ed 7, New York, D Appleton & Co, 1909.

August 6 a further amputation of the left index finger was performed. The patient did not make a satisfactory recovery, the fever continued, with pain in the right lower quadrant of the abdomen and vomiting. At this time, October 1936, there was no evidence of osteomyelitis of the stump. Roentgen study of the gastrointestinal series and of the colon after a barium sulfate enema gave negative results. A retrograde pyelogram of the right kidney at this time was normal. The lungs and heart were normal. Pelvic examination showed retroversion of the uterus but nothing to account for the fever. Repeated blood cultures gave negative results.

The eyegrounds were normal. The basal metabolic rate was -17 per cent. The patient was considered definitely hysterical and at times was suspected of having a psychosis. Psychiatric examination failed to confirm this. The temperature remained between 98.6 and 101 F. The red blood cell count remained near $4,000,000$ and the hemoglobin at 80 per cent. The white blood cell count varied from $6,000$ to $9,000$, and the percentage of polymorphonuclear leukocytes was never above 56 . On October 10 a partly obliterated appendix was removed, and the operation appeared to be without influence on the condition of the patient. After her return to duty the amputation stump of the left index finger remained tender, and from time to time there was a discharge of pus from sinuses which would close in the intervals. The first phalanx of the finger remained.

On June 9, 1937, the patient was again admitted to the Infirmary of the Philadelphia Hospital for Contagious Diseases, because of edema of the ankles and unexplained fever. The white blood cell count was $4,400$, with 39 per cent polymorphonuclears. The temperature subsided, and the patient was discharged on June 18, still presenting an unsolved problem.

Late in 1937 she moved to New York city and was employed as a nurse at the Willard Parker Hospital and later (until March 1938) at the Hudson County Hospital in New Jersey. After April 1 she was employed in the women's surgical service at the New York Post-Graduate Medical School and Hospital. Because of the tenderness and intermittent opening of sinuses in the stump of the finger, she was admitted as a patient on June 21 for surgical revision of this stump, having remained on duty on June 20. At the operation at $5:49$ p. m., June 21, with the patient under nitrogen monoxide and oxygen anesthesia, the old scar was excised. The distal half of the proximal phalanx of the left index finger was found softened and was removed with a rongeur down to the beginning of the articular flare. The wound was sutured, one rubber band being inserted for drainage. The operation was finished in six minutes. No record was made of microscopic or cultural examination of material removed at this operation.

The outstanding features of the subsequent record are shown in figure 1. On return from the operating room the patient was restless, thrashing about in the bed and talking irrationally through the night. Side boards were placed on the bed at midnight. One-sixth grain (0.01 Gm.) of morphine was given at 9 p. m., and this dose was repeated at $1:30$ a. m. The pain in the hand seemed beyond control. In addition, there was severe general itching, apparently unexplained. Her complaints were so out of proportion to the visible evidence of disease that she was considered hysterical. Sedatives were employed frequently every day. She was up in a chair on June 23, but on June 24 her pulse rate reached 130 and her temperature 100 F. On this date the following progress note was made: "The patient appears critically ill—dehydrated." On the next day the dressings were removed from the finger, and daily soaks of the hand in hot saline solution were instituted. On June 28 she walked to the bathroom, and on her return she became dizzy and fell to the floor, without evident injury. After removal of the drain, on June 29, she seemed more comfortable. On July 1 she tried to walk again.

but was unsteady on her feet, and that evening she was depressed and had a prolonged weeping spell, eventually becoming quiet at 2 45 a m. Itching of the skin returned on July 2. She was allowed to be out of bed on July 3 and 4, and her temperature had begun to rise. On July 5 a medical consultant discovered an icteric tint of the scleras and many petechiae, varying from pinpoint size to 2 mm in diameter, over the anterior and lateral thoracic regions and slight tenderness in the right upper quadrant of the abdomen. According to the patient, the spots on the skin first appeared on July 2 and had appeared in crops since then. A blood culture was requested. On July 6 the icterus index of the blood was 18.8, the values for nonprotein nitrogen and dextrose were normal. Roentgen examination of the thorax gave negative results. Blood for culture was taken at 8 20 p m, when the temperature had reached 104.4 F. The culture remained sterile. A blood count showed 3,210,000 red blood cells and 3,650 white blood cells per cubic millimeter, with 69 per cent polymorphonuclears. During the next few days there was persistent severe headache, for which an ice cap was used continuously. The patient was seen by various consultants, and the medical consultants agreed on a diagnosis of septicemia. The pain in the right upper quadrant of the abdomen continued and became more severe. A culture of blood taken on July 8 yielded on July 12 3 colonies of *Staphylococcus aureus* per cubic centimeter of blood. Meanwhile, on July 7, intravenous infusion of 5 per cent dextrose, 2 liters per day, was instituted, and a transfusion of 360 cc was given on July 9. Exudate from the wound on the finger was taken for bacteriologic study on July 10, and *Staphylococcus aureus* was found in pure culture.

On July 11 blood was taken for culture at 1 45 p m. The culture showed 44 colonies of *Staphylococcus aureus* per cubic centimeter of blood after twenty hours' incubation and 46 colonies per cubic centimeter of blood after incubation for ninety-six hours. At 1 47 p m on July 11 an intravenous dose of 2 cc of stock asparagine staphylococcus bacteriophage was given and 8 cc of the same phage was needled to the soft tissues of the suppurating finger stump. The patient's temperature rose to 106 F at 8 p m, and at 9 p m blood was taken for another culture, which remained sterile. In fact, all subsequent blood cultures, of blood taken on July 13, 15, 18 and 28, August 11 and 19, September 7 and 26 and October 4 and 7 remained sterile. When, however, the culture of blood taken at 1 45 p m on July 11 showed 44 colonies per cubic centimeter of blood on the following morning, it was decided to administer bacteriophage in a series of doses to induce a shock reaction. Intravenous injections were given as follows: 8 47 a m, 2 cc; 9 25 a m, 3 cc; 10 03 a m, 5 cc; 10 48 a m, 7 cc; 11 25 a m, 10 cc; 12 04 p m, 13 cc; 12 40 p m, 15 cc; 1 24 p m, 20 cc; 2 03 p m, 25 cc; 2 47 p m, 30 cc; 3 32 p m, 30 cc; and 4 16 p m, 40 cc. This made a total of 200 cc of the stock asparagine staphylococcus bacteriophage given intravenously in seven hours and twenty-nine minutes. The temperature was found to be 107 F just after the last injection was given. At 5 p m it registered 108 F, and at 6 p m it was 110.2 F, with a respiratory rate of 42 and a pulse rate of 100. After an alcohol sponge the temperature was 108 F (about 6 30 p m). The patient then had a chill lasting three minutes. At 7 p m the temperature was down to 104.2 F, and at 8 p m it reached its peak at 113 F. Several rectal thermometers were broken before it was possible to get one with a sufficiently long column. The skin was burning hot. The temperature observations were taken under the eye of a physician and are valid without question. A tepid sponge with 50 per cent alcohol was followed by temperatures of 108.4 F at 9 p m, 109.4 F at 10 30 p m and 109.4 F at 11 p m. Rectal irrigation with ice water was proposed and was discarded as too dangerous. An intravenous infusion of 5 per

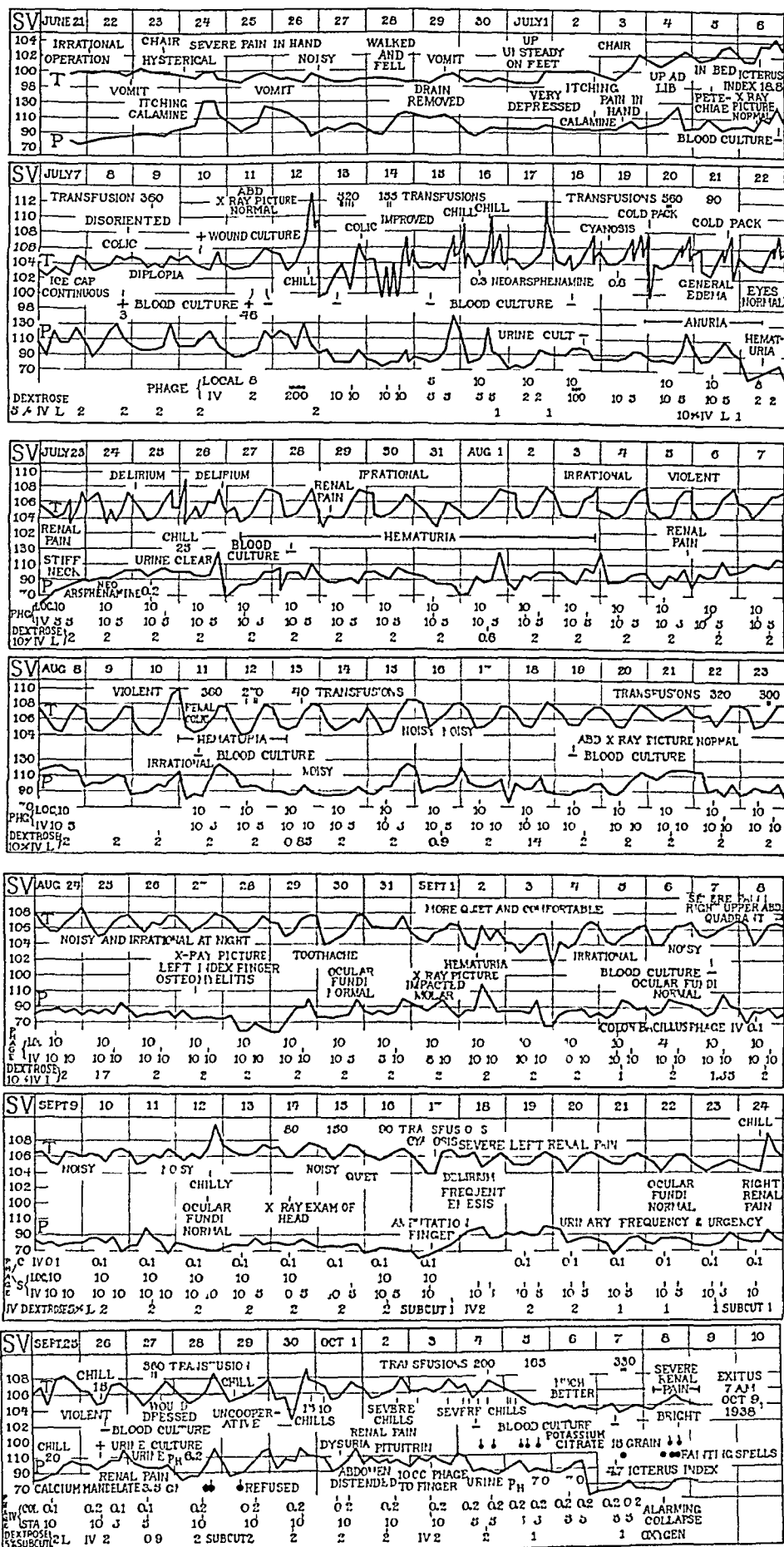


Fig 1—Abbreviated clinical record of S V The maximum temperature of 113 F was reached on July 12, after intravenous injection of 200 cc of staphylococcus bacteriophage in divided doses There were anuria from July 19 to July 22 and hematuria from July 27 to August 3 Bacteriophage was administered intravenously and locally once or twice on almost every day, and dextrose solution in physiologic solution of sodium chloride was given intravenously, usually 2,000 cc per day The left index finger was disarticulated at the base of the first phalanx on September 17 After this there was aggravation of the urologic symptoms

cent dextrose in saline solution at room temperature was started at 10 45 p m, and at 11 30 this was chilled by application of ice bags to the infusion tube. A total amount of 2,000 cc was given from 10 45 p m to 2 00 a m. At midnight the temperature had come down to 99.4 F, and the infusion was allowed to proceed at room temperature. At 1 00 a m the patient's temperature was 99.6 F, at 3 00 a m, 102, at 4 00 a m, 100, and at 6 30 a m, 103. Catamenia began at 10 45 p m, July 12, and there were complaints of pelvic cramps in the early morning of July 13, but the patient slept for a while after 11 p m, and on the morning of July 13 she seemed none the worse for her extreme febrile reaction. Her blood pressure was 108 systolic and 75 diastolic. Transfusion of 520 cc of citrated blood in divided doses (fractional transfusion) was given during the day and 155 cc on July 14. The patient seemed distinctly better, but the temperature would not stay down. Bacteriophage by intravenous injection morning and evening was continued in 10 cc doses, stock phage on July 13 and specific phage in 10 cc doses on July 14, then reduced to 5 cc doses on July 15 and 16 and to 2 cc doses on July 17. The temperature rose to 112 at 8 p m July 17, suggesting that these smaller doses were inadequate.

On Monday morning (July 18) a progress note was made. "The patient appears bright. She seems tired but not exhausted. The heart sounds are rather weak and the pulse relatively slow. The blood pressure is 108 systolic and 78 diastolic. The relatively slow pulse with such high temperatures suggests a possible purulent lesion within the cranium. It seems certain that there are pyemic abscesses. Tenderness in the right side, over the upper pole of the right kidney, suggests that this may be one site of abscess. The liver seems not to be enlarged. The neck is not rigid." A series of doses of phage to a total of 100 cc was given intravenously on this day.

Because of the persistent fever, intravenous injections of neoarsphenamine were given, 0.3 Gm on July 16 and 0.6 Gm on July 19. From 10 p m on July 19 to 11 30 a m on July 22, a period of about sixty hours, no urine was passed and percussion of the lower part of the abdomen did not reveal any dilatation of the bladder until near the end of the period. The urine passed naturally at 11 30 a m July 22 was red with blood. Ophthalmologic consultation on July 22, with careful examination of the fundi, revealed no evidence of abnormality. On July 23, however, the neck was slightly rigid, and a medical consultant recommended spinal tap, which was not done. Dextrose solution, 10 per cent in saline solution, was given daily, 2 liters every twenty-four hours, and the urine became free from blood on July 25. Another intravenous injection of neoarsphenamine (0.2 Gm) was given on July 25. That night there was a chill lasting twenty-five minutes and a rise in temperature to 109 F and from July 27 to August 3 there was always blood in the urine. It was decided to discontinue the arsphenamine.

A progress note on July 30, 1938, at 9 45 a m included the following data: "The patient appears bright and chatty, which is remarkable in consideration of her temperature. Her circulation is good. The urine passed at 5 a m contains red blood cells, about 20 per high power field in the fresh specimen. The absence of pus is remarkable and suggests that the blood may be due to something else than a renal infarct, possibly to a concretion or to diffuse toxic nephritis. One is therefore persuaded that the tenderness below the ribs in the back may be of hepatic rather than renal origin. *Staphylococcus aureus* was abundantly present in the specimen of blood taken for culture on July 11, 1938, but cultures of four specimens taken since bacteriophage therapy was begun have remained sterile. The continued high temperature with hyperpyrexia at night would seem to be related to lesions in the brain, probably several small abscesses or a single

larger one in a region influencing heat regulation. There seems to be reason to hope that this lesion may be gradually walled off and organized by continuation of the present program. The urinary bleeding seems to have some relation to the administration of neoarsphenamine, and the use of this drug is being discontinued for the present."

On August 8 it was decided to discontinue the bacteriophage treatment, and on August 10 the patient was obviously much worse. At midnight her temperature reached 110 F and blood again appeared in the urine. On the next morning there was rather severe renal colic. Bacteriophage treatment was renewed at 10 a m and continued daily. Blood was given intravenously, 360 cc on August 11, 270 cc on August 12 and 40 cc on August 13.

The daily routine at this time included irrigation of the finger stump with 10 cc of phage, the intravenous injection of phage morning and afternoon and the intravenous administration of 2 liters of 10 per cent dextrose in saline solution, later changed to 5 per cent dextrose in saline solution (September 10). The patient vomited part of every feeding, but her nutrition was remarkably well maintained. There was no emaciation. She was delirious and sometimes violent at night but nearly always rational during the day. Severe headache was persistent, and an ice cap was used continuously. On August 13 menstruation was evident, and on August 14 there were numerous swollen red wheals on the face. On August 15 and thereafter the patient was taken out on the roof for about a half-hour almost daily, and from September 21 to October 7 she was given daily treatment with ultraviolet rays.

Roentgen examination of the abdomen on August 20 gave negative results, and similar examination of the finger stump on August 27 revealed continuing osteomyelitis. The ocular fundi were examined by two consultant ophthalmologists on July 22, September 6, September 12 and September 22, without any positive findings. Roentgen examination of the head on September 14 revealed a slight accentuation of the lateral or sigmoid sinus on the left side, beginning back of the mastoid and extending almost to the median line. Some of us, who were familiar with the clinical behavior of the patient, were inclined to think that the obscure outline of the torcular Herophili, of the posterior portion of the superior longitudinal sinus, of the occipital sinus and of the mesial portion of the right lateral sinus might point to swelling of the brain substance and possible abscess of the brain located near the torcular Herophili and somewhat to the right of the median line. The evidence was not, however, accepted as convincing.

After fractional transfusions on September 14, 15 and 16 the patient seemed to be improved, and on September 17, with the use of cyclopropane anesthesia, the proximal phalanx of the left index finger was disarticulated at the base. This operation had been postponed for several weeks because of the critical state of the patient, and when it was finally done the reaction was unfortunate. The complaints of pain seemed in part hysterical. Frequent doses of codeine and of morphine were given on September 17, 18 and 19. On September 19 the morphine was discontinued. Most alarming was the development of severe pain over the left kidney associated with spasm of the left abdominal wall, even while the patient was receiving the sedatives. Atropine was given for several days. On September 24 there were a chill and a rise in temperature to 109 F. The perirenal pain extended to the right side. A culture of urine taken on September 26 yielded abundant colonies of the colon bacillus (approximately 2,000,000,000 organisms per cubic centimeter) but none of staphylococci. This colon bacillus was not fully susceptible to the stock colon bacillus phage which was in use, a specific bacteriophage, therefore, was prepared, and its injection was begun on Oct. 3, 1938.

Administration of calcium mandelate in doses of 3.5 Gm four times a day was started on September 28, but the patient refused to take this on September 29, and it was discontinued. Her condition became less satisfactory, and there were severe chills at frequent intervals from September 30 to October 5, with marked abdominal distention on October 1 and 2. On October 3 the specific colon bacillus phage was given intravenously in place of the stock phage previously used, and on October 4 potassium citrate was given to render the urine neutral. As soon as this was accomplished the patient felt better. Unfortunately the citrate was discontinued for two days, and the severe renal pain returned at 4:30 a. m. on October 8. The



Fig. 2—Roentgenogram of the back of the head, taken on September 14. The interpretation was problematic, and the roentgenogram was considered normal.

patient went into alarming collapse at 10:30 a. m. and was resuscitated by artificial respiration. She died early the following morning, October 9.

The jaundice which had been present in June, with an icterus index of 18.8 on June 6, had entirely disappeared, so that the icterus index on October 7 was 4.7 (normal).

Blood counts during the course of the illness had shown a remarkable lack of leukocytosis, but there was some leukocytic response to the acute infection of the urinary tract at the end of September. The severity of this infection was also evidenced by the rapidly developing anemia, as was shown by examination of the blood on October 4.

The remarkable feature was the long-continued high temperature. The possibility of fraud was given some consideration. We were inclined to exclude this, because the highest temperatures were observed by several persons present at the time and were associated with delirium. Trickery by the patient would be difficult to explain, because her left hand was covered with surgical dressings and an infusion of dextrose was running into a vein of the right forearm on many occasions while the rectal temperature was being taken. Friction by contraction of the anal sphincter was checked by simultaneous observation of rectal and oral temperatures, which checked reasonably well (on one occasion the rectal temperature was 104 F and the oral temperature 103.4 F, on another occasion the former was 105.2 F and the latter 104.6 F). Unfortunately, the temperature of the freshly voided urine was not tested an oversight which we regret. Hysteria may present difficult puzzles. However, the neurologic consultants found no evidence of genuine hysteria, and such manifestations as prolonged anuria and hematuria and eventual death are not easily ascribed to hysteria, particularly in a patient confined

Examinations of the Blood

Date	Hemoglobin		Red Cells	White Cells	Percentage	
	Grams	Percentage			Polymorphonuclears	Lymphocytes
July 6	10.8	65	3,210,000	3,650	69	29
July 8	11.4	68	3,780,000	3,500	59	35
July 12 (a m)				1,775	76	39
July 12 (4 35 p m)				3,775	76	39
July 13 (9 10 a m)				2,825	59	56
July 15	13.2	79	1,210,000	4,650	75	43
July 18	12.2	73	1,420,000	6,200	52	46
July 22	15.6	94	1,720,000	3,875	70	43
July 28	14.0	84	4,260,000	4,100	67	32
Aug 8	11.0	66	3,600,000	6,200	73	24
Aug 18	10.5	63	3,640,000	4,600	40	50
Aug 31	13.0	78	3,910,000	5,200	38	56
Sept 9	11.7	70	3,810,000	5,000	42	51
Sept 26	11.4	68	3,600,000	8,850	65	29
Oct 1	9.0	54	3,360,000	3,200	57	40

to bed and deprived of the use of her hands. It should be mentioned that the intravenous dextrose solution was given slowly because the patient vomited when it was given at the usual rate. Ordinarily the infusion was started about 2 p m and completed at midnight or shortly thereafter, and during this time any extensive movement was precluded. The patient cooperated well in this matter. Reinsertion of the infusion needle was not a simple and easy technical procedure in this case.

Necropsy was unfortunately delayed for twenty-six hours because death occurred early on Sunday and there was delay in obtaining permission from a relative far away. The well developed body showed no evidence of loss of weight. The finger tips were cyanotic, and there was a healing wound at the site of amputation of the left index finger. Edema of the extremities was absent.

There were marked cerebral edema and small areas of pial hemorrhage in the left frontal and parietal areas. On section there was marked congestion, particularly in the right basal ganglions and in the pons. In the left cerebellar medulla an irregularly outlined cavity occupied the major portion of the site of the dentate nucleus, the outer margin of which was distinctly recognized. The cavity extended to the right to involve the medial portion of the right dentate nucleus. Microscopically, disintegrating brain substance without evidence of reaction lined the cavity. Bacterial rods were seen in many sections, especially in those of the cerebellum.

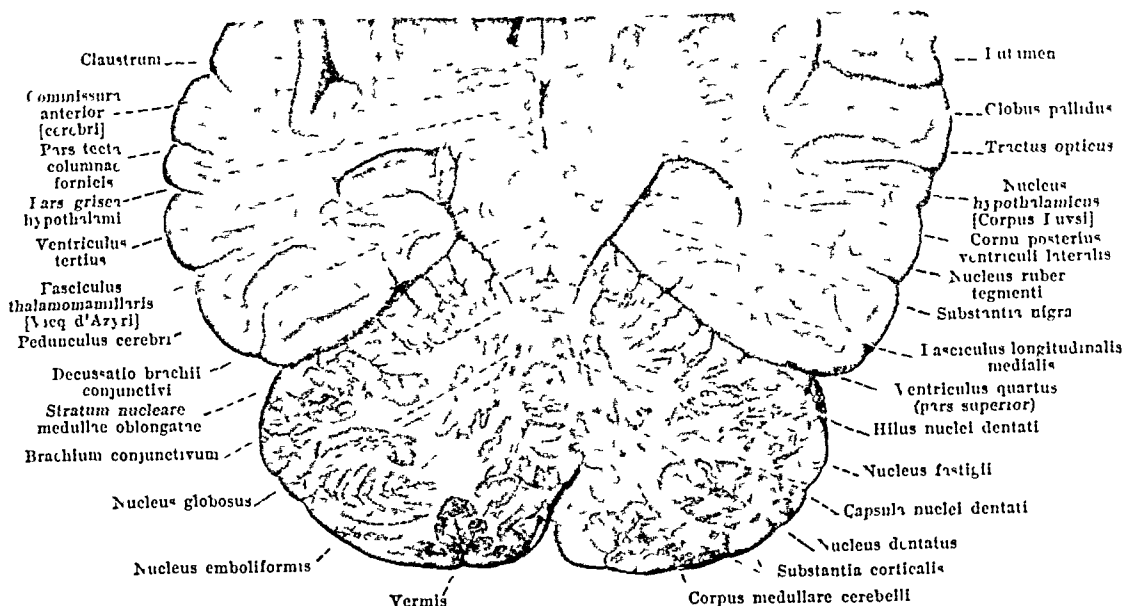


Fig 3—Section of the normal human brain, showing the nucleus dentatus, nucleus emboliformis and nucleus globosus and their relations (Spalteholz, W Hand-Atlas of Human Anatomy, ed 2, translated by L F Barker, Philadelphia, J B Lippincott Company, 1906, vol 3, p 666, fig 744)

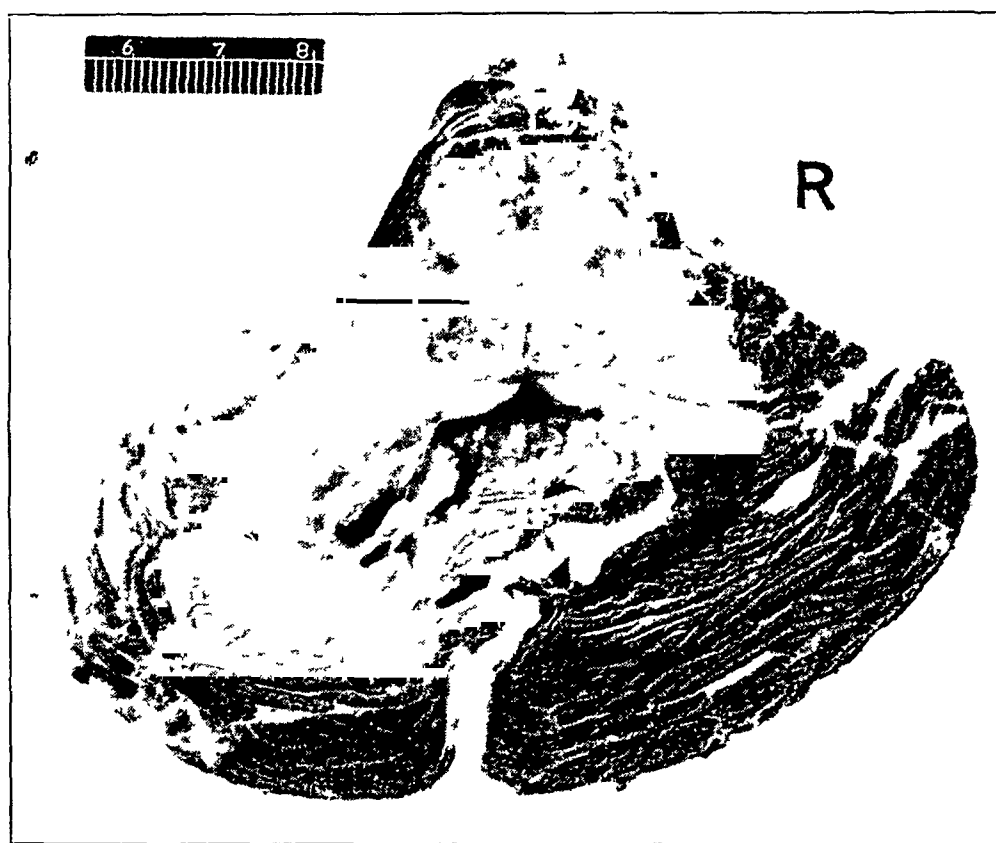


Fig 4—Section through the cerebellum of S V, showing an irregular cavity involving the posterior part of the right dentate nucleus, the mesial portion of the left dentate nucleus and the posterior portion of the intervening vermis

Pulmonary edema was present. Myocardial degeneration, fibrosis and hypertrophy were seen in moderate degree, as well as coronary arteriosclerosis and aortic atherosclerosis. In the pancreas there were diffuse fibrosis and prominent hyalinization of the islets of Langerhans. In the kidneys there was acute pyelonephritis, most marked in the renal substance. The pelvic area presented evidence of an older process, with scarring, thickening and focal collections of lymphocytes and fewer plasma cells. There was also chronic cystitis.

The irregular cavity in the cerebellum excited great interest, but its nature was not established. The possibility that there may have been a relatively benign glioma of the type of astrocytoma fibrillare, with cystic degeneration, was considered. Such a tumor may exist for years and may sometimes be associated with vague nervous manifestations and complaints leading to abdominal and pelvic operations. Special studies of the cerebellar tissue about this cavity failed to reveal any convincing evidence of such a neoplasm.

COMMENT

Hyperthermia is sufficiently rare to constitute a challenge to careful and precise observation. This patient was studied with unusual care, and no effort was spared to bring about her recovery. However, those caring for her had other duties, and there was not much spare time for nonessentials.

In study of the record, one may conclude that the high temperatures recorded were fabrications due to trickery of the patient or to carelessness of the observers, that the patient was a chronic malingerer, that the irregular cavity in the cerebellum was entirely due to postmortem disintegration and that the edema of the cerebral cortex and the hemorrhages in the basal ganglions were entirely agonal. Such a conclusion would lead one to discard the case altogether. As one physician put it: "Such temperatures would occur only in a nurse."

Most physicians, however, are inclined to accept bedside records as reasonably reliable. Perhaps we may be too gullible, but we do not think so. Those who were in personal contact with this patient during life found no reason to suspect trickery. There was some consistency in the observations. One may assume that the amputation on June 21 had dislodged some staphylococci and permitted their transportation to the cerebellum, where a destructive lesion slowly developed. Her fall on June 28 while walking and her unsteadiness on July 1 were suggestive of a cerebellar lesion. The itching was evidently associated with icterus, and this in turn was related to the sepsis. The invasion of the blood stream by *Staphylococcus aureus* was convincingly proved by cultures of blood taken by two different persons on July 8 and 11 and seeded in each instance into two flasks of broth and three agar plates. The remarkable rise in temperature on July 12 resembled closely the response to bacteriophage therapy in sepsis, but in this instance it was excessive. At this time the body was hot and the patient was irrational. The subsequent temperature record was highly atypical considering

that blood culture was negative after bacteriophage sterilization of the blood stream, and it suggested a localization in the brain. Roentgen studies on September 14 revealed irregularities in the dural sinuses suggesting, but not proving, alteration of pressure relations in the cerebellum. At necropsy the brain revealed evidence of disturbed pressure relations, with edema of the cerebral cortex, congestion and extravasations of blood in the basal ganglions and an irregular ragged cavity in the cerebellum. Postmortem changes obscured the picture, and the nature of this cavity remains uncertain. It is, however, possible that it may have marked the site of a staphylococcic abscess which had become sterilized and quiescent, only to be again invaded by the colon bacilli in the terminal days of the illness. The terminal phenomena, particularly the respiratory collapse on October 8, might well have resulted from compression of the medulla, forcing it downward into the foramen magnum.

If this view of the record is accepted, this case would seem to shed some light on the problem of hyperthermia. It is a matter of sincere regret that the clinical observations have not been critically exact and that the necropsy study leaves something to be desired. Nevertheless, cases of hyperthermia are so rare and the subject is so important and still so obscure that a detailed record seems justified.

SUMMARY AND CONCLUSIONS

Hyperthermia remains a controversial problem.

Temperatures in man above 46 C (114.8 F) should not be accepted as genuine without most critical examination of the evidence. There are sound theoretic and experimental reasons for this attitude.

Temperatures in man between 42 C (107.6 F) and 46 C (114.8 F) should be subjected to skeptical and critical scrutiny. Such observations should be supported by testing with multiple thermometers held by reliable observers simultaneously in the axilla, the mouth and the rectum and by observations of the temperature of the freshly voided urine and feces. While many reported observations in this range are undoubtedly genuine, there are also some reports in this category which are highly questionable.

Records are presented of a patient who had prolonged hyperthermia. She eventually died and necropsy was performed. Unfortunately the observations were not adequately checked according to the methods just described, but they are believed to be valid.

At necropsy there was found an irregular cavity of problematic nature in the cerebellum near the left dentate nucleus.

MULTIPLE MYELOMA

ASSOCIATED WITH NODULAR DEPOSITS OF AMYLOID IN THE
MUSCLES AND JOINTS AND WITH BENCE
JONES PROTEINURIA

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AND

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The occurrence of typical and atypical amyloidosis associated with multiple myeloma is now well recognized¹ Atkinson² in a review of 643 recorded cases of multiple myeloma found amyloid reported in 40, or an incidence of about 7 per cent Unusual amyloid tumor formation and localization are cited by Helly,³ Randall,⁴ Glaus⁵ and Askanazy⁶ The cases of multiple myeloma in which amyloidosis is atypical in its distribution or type are considered in this paper In them, besides the underlying myeloma, there are amyloid masses in varying number and size distributed throughout the body In certain cases the amyloid is found particularly in the voluntary musculature and in the joints, so that the clinical picture closely resembles that of rheumatoid arthritis A survey of the literature reveals that there have been only 11 recorded cases of this type It will be noted from the table that those first reported in the American literature were described by Michelson and Lynch⁷ in 1934 and

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1 Magnus-Levy, A (a) Bence-Jones Eiweiss und Amyloid, *Ztschr f klin Med* **116** 510, 1931, (b) Multiple Myelome VII Euglobulinämie, *Zur Klinik und Pathologie, Amyloidosis*, *ibid* **126** 62, 1933

2 Atkinson, F R B Multiple Myelomata, *M Press* **195** 312 and 327, 1937

3 Helly, K, in Henke, F, and Lubarsch, O *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1927, vol 1, pt 2, p 1063

4 Randall, O S Multiple Myeloma Complicated by Intestinal Obstruction, *Am J Cancer* **19** 838, 1933

5 Glaus, A Ueber multiples Myelozytom mit eigenartigen zum Teil Kristallähnlichen Zelleinlagerungen, kombiniert mit Elastolyse und ausgedehnter Amyloidose und Verkalkung, *Virchows Arch f path Anat* **223** 301, 1916-1917

6 Askanazy, M Ueber knotchenformige lokale Amyloidbildung in der Darmmuskulatur, *Verhandl d deutsch path Gesellsch* **7** 32, 1904

7 Michelson, H E, and Lynch, F W Systematized Amyloidosis of Skin and Muscles, *Arch Dermat & Syph* **29** 805 (June) 1934

Rosenblum and Kirshbaum⁸ in 1936. In neither of the cases was an autopsy performed. We herewith report a case with complete clinical and postmortem study.

Tumor-like masses of amyloid in association with multiple myeloma have been described by Hueter and others, as shown in the accompanying table. In cases in which an autopsy was performed the anatomic observations were very similar to ours. Hueter⁹ aptly described the amyloid material in the tumor masses as resembling fish flesh. The amyloid in the joints resembled closely that seen in our case, both grossly and microscopically. It is noteworthy that in the cases collected from the literature, as well as in ours, there was scant deposition of amyloid in the liver, spleen and kidneys. This lack of involvement of the usual sites is characteristic of most atypical amyloidosis. It is particularly characteristic of the condition designated as primary amyloidosis,¹⁰ accompanying which there is no recognized disease.

REPORT OF A CASE

A white woman 45 years old was first seen in the medical clinic of the New York Hospital on March 4, 1935. She complained of having had (1) an ache in the lower part of the back for years, (2) pain in the back of the neck and shoulders during the past years and (3) spells of weakness and fever during the past two weeks.

Her past medical history revealed typhoid fever at the age of 20, diphtheria at 24 and attacks of influenza at 24 and 28.

Her family history was irrelevant.

Examination—Her temperature was 98.6 F., and her pulse rate, 80 per minute and regular. Her blood pressure was 130 systolic and 80 diastolic. Careful physical examination by different observers disclosed nothing significant.

Laboratory investigation revealed a negative Wassermann reaction of the blood, a red blood cell count of 4,000,000, with 72 per cent hemoglobin (Dare method) and 12,000 white blood cells, with a normal differential count. The urine on the first examination gave a 4 plus reaction for albumin but showed no sugar. Microscopically, clumps of white blood cells were observed. On two other occasions the routine laboratory examinations showed a 1 or 2 plus reaction for albumin, with a varying number of polymorphonuclear leukocytes. The basal metabolic rate was -12 per cent.

In view of the findings a tentative diagnosis of pyelitis was made. On cystoscopic examination intravenously administered dye appeared within two to three

8 Rosenblum, A. H., and Kirshbaum, J. D. Multiple Myelomas with Tumor-Like Amyloidosis. Clinical and Pathologic Study, *J. A. M. A.* **106** 988 (March 21) 1936.

9 Hueter, C. Ungewöhnliche Lokalisation der Amyloidsubstanz in einem Falle von multiplem Myelom (Amyloid des Darms, der Thoraxmuskulatur, des Schultergelenks), *Beitr. z. path. Anat. u. z. allg. Path.* **49** 100 1910.

10 Lubarsch, O. Zur Kenntnis ungewöhnlicher Amyloidablagerungen. *Virchows Arch. f. path. Anat.* **271** 867 1929.

Summary of Cases of Amyloid in Association with Multiple Myeloma

Case	Age and Sex	Author	Striated Muscles	Joints	Joint Spaces	Bence Jones Protein	Kidney	Comment
1	58 M	Hueter ⁹	Large masses in deltoid, serratus magnus	Left shoulder, others not examined	Numerous free masses of amyloid	+	Contracted, condition regarded as nephritis	Myeloma, regarded as cause of amyloid
2	39 M	Zeehuisen ¹¹	Countless masses of varying size	Numerous joints	Not mentioned	42 Gm daily for three weeks	Not mentioned	Cited by Magnus Levy
3	46 M	Buch ¹²	Numerous large masses	Shoulders and hips	Filled with amyloid	?	Not mentioned	Cited by Magnus Levy
4	?	Wiessner ¹³	Diffuse muscular involvement	Hips, knee joints	Filled with amyloid	?	Not mentioned	No clinical data
5	46 F	Magnus Levy ¹	In inguinal region	Shoulders, hands, knees, sterno clavicular joints	Numerous masses	++	Chronic "nephrosis"	Diagnosed in life, proved by autopsy
6	56 M	Magnus Levy	None visible	Shoulders, elbows, fingers stiff	Not examined	+	Not mentioned	No autopsy
7	57 M	Paul ¹⁴	Jaw muscles, tongue, pharynx, masses	Shoulder	Not examined	+	Not mentioned	Extensive amyloidosis
8	38 F	Paige ¹⁵	Large masses in both deltoids	Shoulders and sternoclavicular joints	Glenoid fossa (small amounts)	+	Involved by amyloid	Extensive amyloidosis in all organs except liver
9	54 M	Michelson, Lynch ⁷	Macroglossia, cutaneous amyloid	Hips, hands	Not examined	+	Clinically diminished function	Roentgenograms similar to those of case 12, no autopsy
10	39 F	Rosenblum, Krashbaum ⁸	Chest muscles, masses	Pain in hips and spine, stiffness of joints	Not examined	+	Patent died in uremia	Clinical diagnosis, biopsy and roentgenograms, no autopsy
11	38 M	Stewart ¹⁶	Large masses over body	Numerous joints	Not examined	+	Not mentioned	Clinical report, no autopsy
12	45 F	Tarr and Ferris	Numerous masses in muscle attached to bone	Numerous	Filled with amyloid	+	Nephrosclerosis	

¹¹ Zeehuisen, H. A. Case of Albumosurie, Nedertl tijdschr v geneesk ²⁹ 829, 1893, cited by Magnus-Levy ^{1a}
¹² Buch, H. Ein Fall von multipler Sarcomatose des Knochenmarkes, und eine eigenthumliche Affection der vier grossen Gelenke, Dissert., Halle, Lipke, 1873, cited by Magnus Levy ^{1a}
¹³ Wiessner, R., cited in Zentrbl f allg Path u path Anat ⁵⁰ 127, 1931
¹⁴ Paul, F., cited in Zentrbl f allg Path u path Anat ⁵⁰ 127, 1931
¹⁵ Paige, B. H. A Case of Myeloma with Unusual Amyloid Deposition Am J Path ⁷ 691, 1931

minutes from each ureteral orifice. Retrograde pyelograms showed normal renal pelvis. Catheterized urine contained only a few isolated white blood cells. It was not tested for albumin.

At this time fluctuation of the amount of albumin in the urine (reactions ranging from 1 plus to 4 plus), apparently unrelated to the number of white blood cells present, suggested the possibility of Bence Jones proteinuria. The urine was tested with this in mind on May 10 and found to yield a cloudy precipitate at 55 C. This increased in intensity as the heating continued and then diminished slightly on boiling. Filtering the boiling urine yielded a clear solution which showed a cloudy precipitate on cooling to about 60 C. Dilute acetic acid intensified the reaction. Subsequent specimens of urine all behaved in the same fashion.

Roentgen examination of the skull, spine, long bones and chest revealed no significant changes. A blood film on June 3, reviewed by the hematology department, showed 7 per cent young polymorphonuclears, 34 per cent adult polymorphonuclears, 52 per cent lymphocytes, 4 per cent large mononuclears, 2 per cent eosinophils and 1 per cent basophils. The red blood cells showed slight anisocytosis with moderate central pallor. The white blood cells were not obviously increased in number. The percentage of lymphocytes was somewhat increased, with a rare immature lymphocyte. No abnormal white blood cells were seen.

Chemical studies made of the blood on June 4 revealed the following values per hundred cubic centimeters: serum calcium 9.5 mg, total proteins 7.0 Gm, serum albumin 3.3 Gm, serum globulin 2.5 Gm and urea nitrogen 14.0 mg.

Course—Because of all these inconclusive findings, a bone marrow puncture and an intravenous congo red test for amyloidosis were contemplated, but the patient refused to cooperate in any further tests and failed to return to the clinic after June 1935. However, we later learned that there was a steady progression of her symptoms. The pain in the back spread, so that it involved the hips and inner surfaces of the thighs. She also had progressive stiffness of the shoulders, elbows and knees with pain on motion in all these joints. The condition was regarded as arthritis by most of the physicians who treated her in the two and a half years prior to her second admission to the hospital. In June 1937 she was forced to give up her clerical work. For the two months prior to the second admission there were edema of the ankles and puffiness of the face.

On admission to the New York Hospital on Jan. 9, 1938, she was thin, emaciated and acutely ill, with obvious distress on even slight movements. Numerous small shotty nodes were present in the axillae and in the posterior cervical region. The anterior cervical nodes were larger and less firm. No inguinal nodes were palpable. In addition, firm masses of variable size and not tender were seen and felt in different parts of the body (fig. 1). Their symmetric distribution is worthy of note. There was a mass about 3 by 3 cm. just in front of each ear and overlying the mandibular joint. There were smaller, less firm nodules in each antecubital fossa. In each axilla anterior to the lateral border of the scapula were similar, but larger, firm round masses apparently attached to the scapulae. The skin was freely movable over these masses.

The shoulder and elbow joints were stiff but permitted slight motion. The right index finger was semiflexed and stiff. There was limited motion of the hips. The knee joints were enlarged but not fluctuant. The right ulna was rough, and over the middle of this bone was a small firm subcutaneous nodule. Little gross deformity of any joint and only slight tenderness on pressure were noted. Three plus pitting edema extended from the feet to the upper third of the calves. The head was normal in size and shape with no tenderness or defect of the calvarium.

The eyes and the fundi were not remarkable. The heart was found not enlarged on percussion and palpation, and its rate was regular. The blood pressure was 124 systolic and 64 diastolic. The lungs were clear. The abdomen was flat, with the edge of the liver firm and palpable 3 fingerbreadths below the costal border in the midclavicular line. There was tenderness on deep palpation in the left flank. The results of pelvic and rectal examinations were not remarkable. Reflexes were normal.

The disease ran a febrile course. The irregular temperature went to 103 F and the pulse rate to 140. Despite two blood transfusions the patient's progress was steadily downgrade, with death four weeks after admission to the hospital.

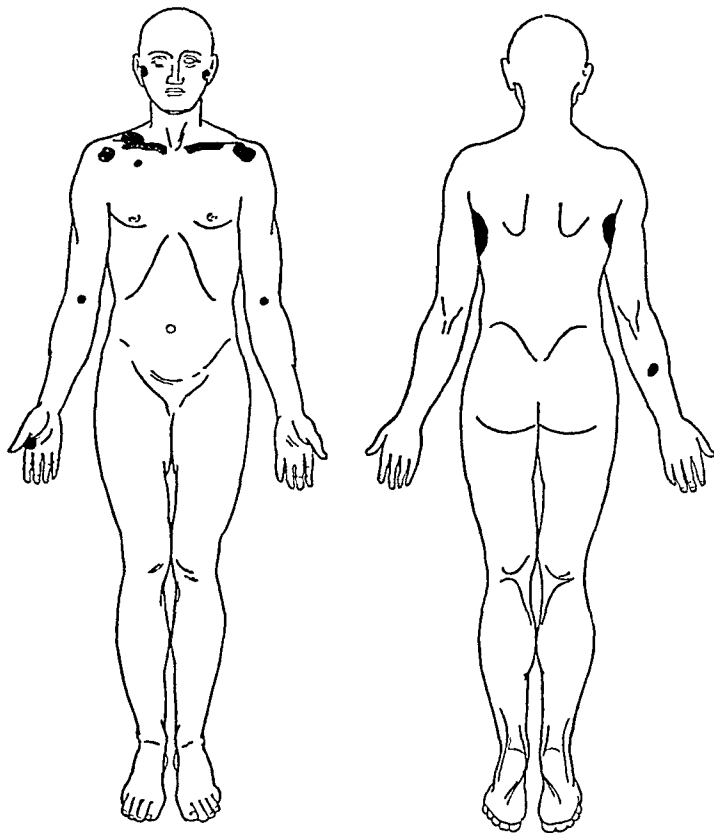


Fig 1—The distribution and relative size of the amyloid tumors, shown in solid black.

Laboratory Studies—A small nodule near the left scapula and one over the right ulna were removed under local anesthesia. The mass near the scapula was found between the muscles. It was yellowish, was of homogeneous structure and when cut showed the consistency of firm gelatin. The nodule over the ulna did not shell out easily and seemed fixed to the underlying structures. Microscopically the pieces appeared similar and were seen to consist of plugs of light-staining hyaline relatively acellular tissue, with a tendency to form whorls. A few small blood vessels were scattered throughout.

Large amounts of Bence Jones protein were present constantly in the urine, and in addition there was a 1 plus reaction for albumin. There were always 20 to 30 white blood cells per high power field, with a few granular casts. The specific gravity ranged from 1.007 to 1.027. A typical blood study showed 2,100,000

red blood cells, with 45 per cent hemoglobin, and 6,000 white blood cells, with 28 per cent adult polymorphonuclears, 30 per cent lymphocytes, 4 per cent monocytes and 4 per cent basophils. Two nucleated red blood cells per hundred white blood cells and occasional plasma cells were seen in the smear (Dr C E Folkner). The erythrocytes showed poikilocytosis, anisocytosis, microcytosis, polychromatophilia, stippling and Cabot rings. The blood coagulation time was ten minutes and the bleeding time two minutes. The clot retraction was excellent and fragility normal. Chemical studies of the blood gave the following results:

	Jan 10	Jan 19	Jan 24	Feb 2
Urea nitrogen, mg per 100 cc	10		26	
Serum phosphorus, mg per 100 cc	3.6			
Serum phosphatase, units	5			
Serum calcium, mg per 100 cc	9			
Serum albumin, Gm per 100 cc	3.1	2.6		2.5
Serum globulin, Gm per 100 cc	0.6	1.1		0.4
Plasma chloride, mg per 100 cc	560			
Carbon dioxide, volumes per cent			46	
Icteric index				5

There was no evidence of Bence Jones protein in the serum filtered at the boiling point and then cooled. A congo red test showed that 72 per cent of the dye was removed from the blood stream in one hour. The normal rate is about 30 per cent in one hour. Renal function tests with phenolsulfonphthalein showed 51 per cent excretion in one hour shortly after admission and 23 per cent one week before death.

Roentgenologic examination on January 10 of the skull, chest and long bones revealed a mottled, somewhat discrete, minute, rounded osteolytic process throughout the proximal ends of the humeri and the femurs, with a suggestion of a similar process in the left frontal region of the skull. Changes in the ribs were not definite. There was evidence of localized demineralization in both femurs, wrists and hands.

Diagnosis—Multiple myeloma had been suspected when the patient was first seen in 1935. The nature of the tumor masses was uncertain, but it was thought that they were part of the underlying disease. In view of the long-standing Bence Jones proteinuria it was believed that there was a definite renal lesion. The peripheral edema was attributed to the severe hypoproteinemia.

Postmortem Examination—An autopsy was performed twenty-four hours after death. General inspection revealed changes essentially the same as those described clinically. Approximately 450 cc of clear yellow fluid was in each pleural cavity.

The heart weighed 280 Gm. There were small deposits of fat beneath the endocardium of the left ventricle.

The lungs weighed 1,500 Gm. They were deep red, and the lower parts were much less crepitant than usual.

The spleen weighed 310 Gm and was not remarkable.

The stomach, intestines and pancreas were without noteworthy change.

The liver weighed 1,680 Gm. On the cut surface the lobular architecture was distinct, with mottled, pale, translucent grayish and light yellow areas.

The adrenals were not remarkable.

The kidneys weighed 135 and 130 Gm and were firm and pale reddish pink. The capsules stripped readily, despite the presence of numerous, diffusely distributed small depressed areas in the cortex from 0.3 to 0.7 cm across. On the cut surface

the usual cortical architecture was not distinct, and the medulla and the cortex were poorly differentiated. In some places the cortex measured only 0.3 cm in thickness. The pyramids were somewhat more translucent and paler than usual.

Aside from a few small scattered hemorrhages in the bladder mucosa there were no changes in the pelvic organs.

The pharynx, larynx, esophagus and thyroid were not remarkable. Two parathyroid glands were found on each side, the right lower one being somewhat larger than the others, and all were uniform in consistency and shape. After fixation in formaldehyde they weighed together 139 mg.

The cut surface of the vertebrae was mottled grayish white and light red. In a few places the soft, lighter tissue formed somewhat indistinctly demarcated nodules, the largest not over 0.6 cm across. The marrow of the sternum and



Fig 2—*A* and *B*, ribs with attached amyloid masses. *A*, Several rounded nodules of myeloma in the longitudinally split rib. *B*, the laminated structure of an amyloid tumor. *C*, the right knee joint, opened, with the patella reflected upward. Villous deposits of amyloid attached to the synovial membrane are most conspicuous at the margins of the patella and near the upper edge of the articular surface of the tibia. Much more similar material was loose in the knee joint.

ribs was of similar appearance (fig 2*A*). The marrow trabeculae of all these bones were softer than usual, obviously owing to partial decalcification. The bones of the skull were hard, and no nodules of tumor or areas of rarefaction were found.

Both knee joints and the right acromioclavicular joint were opened. In the cavity of each knee joint was an increased amount of sticky, reddish fluid. Somewhat gelatinous, translucent pink material formed villous projections from the

synovial membrane and was found free in the joint cavities (fig 2 C) The articular surfaces were not eroded, nor were there deposits on the cartilage The acromioclavicular joint was similar in appearance

Attached to the periosteum of the lateral aspect of the right fifth and sixth ribs was a firm mass that measured approximately 11 by 6 by 2.5 cm On section it was found to consist of layers of generally homogeneous, yellowish pink translucent material suggesting cartilage Some of this substance was easily dislodged in small solid sheets (fig 2 B) A few centimeters posteriorly, attached to the fifth rib, was a smaller mass of similar material, about 2.5 cm across Adherent to the left fifth rib was a mass which measured 10 by 5 by 2 cm It was somewhat firmer than those on the right It contained scattered small yellow foci All of these masses were loosely attached to the ribs so that they could be moved and were not continuous with the bone itself They appeared to push aside the adjacent muscles rather than to invade them Firm, translucent hyaline tissue was intimately attached to the left clavicle near its medial and lateral ends, forming nodular elevations of the surface About the head of the right humerus was a large mass of hyaline material that fused with the periarticular tissue

The lymph nodes near the head of the pancreas were enlarged, firm and somewhat flattened The para-aortic nodes were slightly enlarged and reddish

The pituitary body was not unusual The brain and meninges, aside from slight thickening of the arachnoid in the interpeduncular space, were not remarkable

Microscopic Examination—In one medium-sized artery of the heart the media was extensively replaced by pink-staining homogeneous material resembling amyloid

In the media of a few small blood vessels there was a scant amount of hyaline material In the lumens of the alveoli were many red blood cells and numerous large mononuclear phagocytes containing brown pigment granules Slight bronchopneumonia was evident In one of the larger vessels was a mass of leukocytes, among which were a number of cells resembling plasmacytes

In the spleen the connective tissue was slightly increased In the congested pulp were seen many large mononuclear cells, of which some were apparently myelocytes, while others resembled plasma cells

There was some increase in interacinar and interlobular connective tissue in the pancreas

Fatty vacuolization of the liver cells without zonal distribution was present In the connective tissue of the portal spaces were scattered lymphocytes and larger mononuclear cells, with a few plasma cells

There were focal scars on the cortex of the kidney, increased connective tissue, atrophy of some tubules and dilatation of others In the cytoplasm of some of the convoluted tubules were small hyaline droplets of varying size Sudan IV stain showed a few fatty droplets The tufts of most of the glomeruli in the scars were partially or completely replaced by bright eosinophilic material Many glomeruli in other areas contained smaller amounts In the lumens of the convoluted tubules there was a granular pink albuminous precipitate, while in many of the straight collecting tubules there were masses of more intensely bright eosinophilic granules, or homogeneous casts, formed apparently by fusion of the granules (fig 3 D) The lining epithelium of many tubules was flattened and in places was difficult to recognize Adjacent to the casts were frequently seen large mononuclear cells and large multinucleated cells of the foreign body type In places these giant cells partially surrounded the hyaline material or were in intimate contact with it A pink-staining homogeneous substance resembling

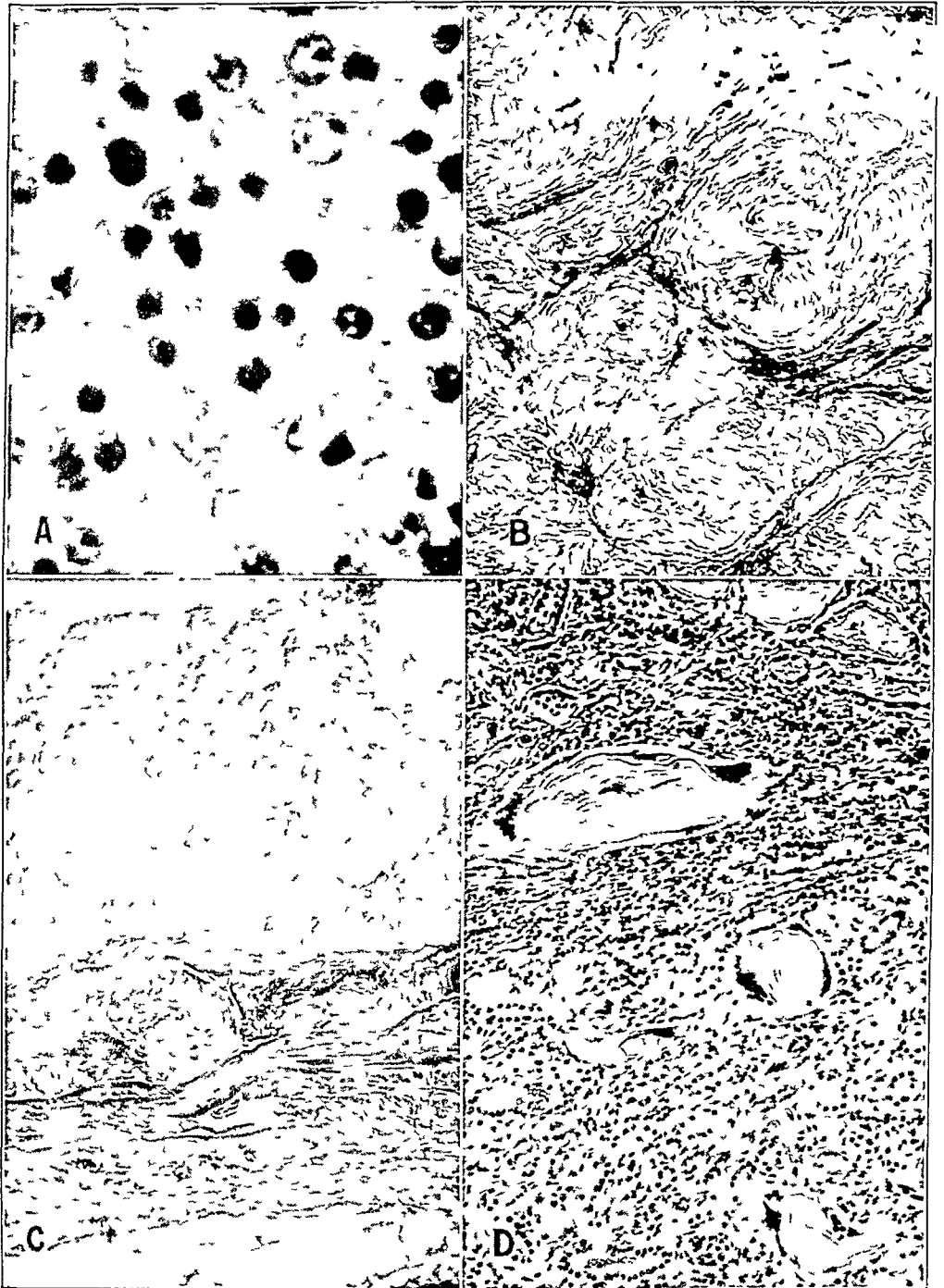


Fig 3—*A*, cells resembling plasma cells in the marrow of the sternum (hematoxylin and eosin, $\times 771$) *B*, nodules of amyloid in one of the masses attached to the ribs, showing delicate trabeculae of connective tissue (Van Gieson's stain, $\times 95$) *C*, distribution of amyloid deposit on synovial membrane of the knee joint, showing lack of involvement of the underlying connective tissue ($\times 25$) *D*, hyaline, partly lamellated casts in the tubules of the kidney. Multi-nucleated giant cells are seen in the edges of the material. There is an infiltration of lymphocytes in the adjacent tissue ($\times 95$)

amyloid was in the media of a few moderate-sized arteries. The capillaries of the medulla contained large mononuclear cells closely resembling plasmacytes.

Practically the whole lymph node of the pancreas was replaced by diffusely distributed large mononuclear cells resembling plasmacytes. Radial arrangement of the chromatin and perinuclear clear zones in the cytoplasm were rarely seen.

In the parathyroids clear cells were not numerous. Several small vessels with thickening of their walls contained deposits of pink hyaline material in their media.

The marrow of the vertebrae and sternum was almost entirely replaced by closely packed cells resembling those found in the pancreatic lymph node (fig 3A). In the femur and ribs were foci of hematopoietic tissue containing cells of the myeloid and erythrocytic series.

The masses attached to the bones were composed of homogeneous or fibrillar material which varied in its staining with eosin from deep to light pink. In it were scattered connective tissue cells. The substance was subdivided into nodules or lobules of varying size by strands of deeper pink (fig 3B). Thin-walled blood vessels were numerous and usually surrounded by delicate strands of connective tissue in which were a few plasma cells and lymphocytes. In a section removed from a nodule attached to the left clavicle were several multinucleated giant cells embedded in the homogeneous material. In the periarticular mass of the right shoulder, pink homogeneous material blended with the cartilage. The pink-staining material described previously was very suggestive of amyloid.

In the knee joints and in the right acromioclavicular joints, masses of pink-staining granular, fibrillar or homogeneous material were attached to, and intimately fused with, the synovial membrane (fig 3C). Into this substance extended delicate strands of connective tissue with a few cells and thin-walled blood vessels. The surface was irregular, and mesothelial cells of the synovial membrane were recognized in only a few areas.

Frozen sections of the kidney and of the masses attached to the ribs, fixed in 4 per cent formaldehyde, were stained with iodine and sulfuric acid, cresylecht violet, gentian violet and acetic acid, and iodine green.

With iodine and sulfuric acid, light brown deposits were seen in many glomeruli of the kidney. The dense casts in the straight and collecting tubules were also brown, the outer layers being usually darker and occasionally greenish blue. The homogeneous material in an extracostal mass was stained greenish blue in contrast to the yellow of the connective tissue, and here similar greenish material was in the walls of several small arteries. These staining reactions suggest amyloid.

With cresylecht violet and with gentian violet and acetic acid, typical metachromatic staining for amyloid was obtained in the kidney. In the costal mass the pink staining of the homogeneous nodules was in sharp contrast with the inconspicuous staining of the connective tissue. Preparations with iodine green failed to give metachromatic staining. Differential stains for connective tissue, after fixation in Zenker solution (prepared with formaldehyde) and embedding in paraffin, were also employed. With Mallory's aniline blue stain the hyaline deposit, wherever found, i.e. in the glomeruli of the kidneys, the walls of the arteries, knee or shoulder joints or masses attached to the bones, took a somewhat lighter blue stain than the collagenous connective tissue. The more granular casts in the renal tubules were bright crimson, and this color was found in the centers of hyaline casts whose outer layers were homogeneous deep blue.

Van Gieson's stain was combined with the Verhoeff stain for elastic tissue. The hyaline material in the connective tissue masses, in the joints and in the renal glomeruli was orange-yellow, in distinct contrast to the bright canary yellow of the epithelial cells and the muscle and the bright red of the collagenous tissue.

The casts in the tubules stained varying shades of yellow and yellowish brown. The droplets in the tubular epithelium were light brownish yellow, in contrast to the brighter yellow of the remaining cytoplasm.

COMMENT

From the clinical point of view this patient's course presented several unusual features. There is little doubt that the bone marrow was involved by the neoplasm when the patient was first examined, yet complete roentgenologic studies failed to reveal it. Even terminally the roentgenogram was not at all conclusive or characteristic of multiple myeloma. Similar roentgenologic findings are mentioned in several of the cases in the literature, notably those of Michelson and Lynch⁷ and of Stewart¹⁶. The condition is easily mistaken for osteoporosis associated with inactivity or inanition.

Studies of the blood in the early stages were disappointing because they gave little information. There was no hyperproteinemia¹⁷ or hypercalcemia. Toward the end of the patient's illness severe hypoproteinemia, with a serum globulin content of 0.4 per cent and a serum albumin content of 2.5 per cent was noted. Hypoproteinemia in the course of multiple myeloma has been described by Chester¹⁸ and is attributed to the degree of undernutrition. The occurrence of an occasional plasma cell in the blood smear was the only significant observation in stained smears of the blood. Plasma cell leukemia has been reported by several authors, including Beck and McCleary,¹⁹ Muller and McNaughton²⁰ and Piney and Riach.²¹

The only constant finding in favor of the diagnosis of myeloma was the Bence Jones proteinuria. In 10 of the 12 cases of multiple myeloma with amyloid tumors recorded in the literature, Bence Jones protein was found in the urine. It was not mentioned in the other two reports. The absence of this substance in the urine in the reported cases of atypical amyloidosis without myeloma is noteworthy.

16 Stewart, A. Myelomatosis, *Quart J Med* **7** 211, 1938.

17 Perlzweig, W. A., Delrue, G., and Geschickter, C. Hyperproteinemia Associated with Multiple Myelomas. Report of an Unusual Case, *J A M A* **90** 755 (March 10) 1928. Bing, J. Some Cases of Hyperproteinaemia, *Acta med Scandinav* **88** 478, 1936.

18 Chester, W. Multiples Myelom und Hypoproteinaemie, *Ztschr f klin Med* **124** 466, 1933.

19 Beck, H. G., and McCleary, S. Multiple Myeloma with Bone Marrow Plasma Cells in the Blood, *J A M A* **72** 480 (Feb 15) 1919.

20 Muller, G. L., and McNaughton, E. Multiple Myeloma (Plasmacytomata) with Blood Picture of Plasma Cell Leukemia. Report of Two Cases, *Folia haemat* **47** 17, 1932.

21 Piney, A., and Riach, J. S. Multiple Myeloma, Aleukemic and Leukemic, *Folia haemat* **47** 37, 1932.

The gradual development of "arthritis" in the course of multiple myeloma should arouse suspicion as to its origin. Clinically the resemblance to rheumatoid arthritis may be very close. (Excellent photographs illustrating the deformities of the joints are found in Stewart's¹⁶ article) The pain and the disability in the joints are caused by the deposition of amyloid in the joint spaces and periarthritic tissue. With the large joints it is at times difficult to decide whether these masses are in the surrounding muscles or are part of the joint. The occurrence of such masses in the voluntary muscles and along the bones offers a clue to the true nature of the pathologic condition in the joints. In our case, the time of the first appearance of the masses was not known, but, judging from their size, it is safe to assume that they were present for from several months to a year. A similar time interval is noted in the cases reported in the literature. The clinical identification of these masses as amyloid is at times difficult. The congo red test may be inconclusive or may even give negative results. In our case the results suggested the presence of amyloid.

From the pathologic standpoint several observations are of interest. The amyloid tumor of the bones was widespread, and, while in a few areas it was composed of somewhat circumscribed small nodules, in general it consisted of a diffuse replacement of the marrow. This is in contrast to the usual formation of distinct nodular masses of tumor in multiple myeloma. The absence of involvement of the skull was unusual. Microscopically the neoplasm was seen to be composed of cells which resembled plasma cells in several respects but were not typical, because in general the cytoplasm was not as homogeneous as that of typical plasma cells and did not contain a conspicuous perinuclear clear zone. However, these cells were similar to those usually found in what is commonly called a plasma cell myeloma. The presence of a few cells resembling plasma cells in capillaries of the kidney and in a blood vessel in the lung confirmed the clinical observation on the blood smear.

The deposition of hyaline frequently laminated material, presumably Bence Jones protein, in the tubules of the kidney and the scarring of that organ consequent on tubular obstruction have been well described by several authors, including Bell,²² who has made an extensive review of the literature. Forbus and his associates²³ have also recorded a case. MacMahon and Magnus-Levy²⁴ have recently described the experi-

22 Bell, E. T. Renal Lesions Associated with Multiple Myeloma, *Am J Path* **9** 393, 1933.

23 Forbus, W. D., Perlzweig, W. A., Parfentjev, I. A., and Burwell, J. C. Bence Jones Protein Excretion and Its Effect upon the Kidney, *Bull Johns Hopkins Hosp* **57** 47, 1935.

24 MacMahon, H. E., and Magnus-Levy, A. Renal Lesions in Experimental Bence Jones Proteinuria, *Am J Path* **12** 763, 1936.

mental production of renal lesions in rats by injection of Bence Jones protein. They found deposits in the tubules which took a golden orange with Mallory's aniline blue stain. They found similarly staining granules in the cytoplasm of the cells lining the tubules and assumed that they were related to the material in the lining of the tubules. Although it was not specific, they thought this stain of importance in identifying the substance. This belief was not confirmed, however, by Forbus.²⁵ It is noteworthy that in our case part of the tubular deposits took a deep crimson with Mallory's stain, a reaction not obtained with any of the other hyaline deposits in the case. The staining blue of the outer layers of many of the casts, a reaction shown by amyloid, is of interest in view of the relation of Bence Jones protein to amyloid, as suggested by Magnus-Levy.¹ He expressed the belief that in multiple myeloma the protein acts as the mother substance to the amyloid. He has demonstrated in stained specimens what appears to him a gradual transition of one to the other. Experimental evidence to confirm this suggestion was not found by MacMahon.²⁶ With the Van Gieson stain we found no consistent differential staining of the casts. With iodine and sulfuric acid and the metachromatic stains the casts which were not distinguishable from amyloid in their reactions, though they varied in intensity of staining. The occurrence of multinucleated giant cells in close relation to the tubular casts indicates the insoluble nature of the material and suggests that it was present for some time in the tubules. It conforms with the belief that the cortical scars are directly the result of obstruction and stasis. The presence in the renal glomeruli of homogeneous material which gave typical reactions to several of the tests for amyloid complicates the renal picture. Accompanying this is hyaline droplet degeneration of the cells of many of the convoluted tubules, a change often found with renal amyloidosis. None of the droplets stained a golden orange with Mallory's aniline blue, as described by MacMahon in his animals, but with Van Gieson's stain they took a color distinctly different from that of the remainder of the cytoplasm, and with aniline blue many were bluish.

Chemical studies of amyloid tumors²⁷ have revealed no constant composition of the material. It is probable that differences exist between the amyloid found in the liver, spleen and kidney in the usual widely distributed disease and that in the atypical localized deposits. These differences may explain the variations in staining reactions so often observed.

²⁵ Forbus, W. D., in discussion on MacMahon and Magnus-Levy.²⁴

²⁶ MacMahon, H. E., in discussion on Robertson, H. E., and Brunsting, L. A. Amyloidosis with Unusual Distribution and Bence Jones Protein, *Am J Path* **12** 767, 1936.

²⁷ von Bonsdorff, B. Zur Kenntnis der atypischen Amyloidose, *Arch path Inst d Univ Helsingfors* **7** 369, 1933.

SUMMARY

Eleven cases of multiple myeloma with accompanying tumor-like deposits of amyloid in the striated muscles, and with amyloid in and about the joints, are recorded in the literature. The twelfth case is reported here.

In these cases amyloid was not abundant in the usual sites and frequently had atypical staining reactions.

Bence Jones protein was found in the urine in all the cases in which its presence or absence was recorded.

Clinically the involvement of the joints and muscles by the amyloid masses may simulate rheumatoid arthritis.

NOTE—Since the case report presented in this article was submitted for publication, there was admitted to the wards of New York Hospital a 38 year old Negro with a history of arthritis involving the joints of both upper and lower extremities, of five years' duration. The deformity of the joints was striking. There were masses of firm to semi-fluctuant nodes varying from 1 to 10 cm. in diameter and, in addition, many firm subcutaneous nodules in the forearms. The tongue was larger than normal and showed ulceration along its margins. A biopsy of material from the sternum proved the existence of plasma cell myeloma in the bone marrow. Biopsy of the nodes in the forearm and tongue showed atypical amyloid deposits, with a staining reaction similar to that in the case reported. There was serious impairment of renal function, with marked albuminuria for the past year. Bence Jones proteinuria was observed inconstantly. The roentgenograms of all the bones closely resembled those in the case reported except that there was evidence of a destructive process in one vertebra. The results of examination of the blood were of interest. The congo red tests showed 60 per cent retention in the blood stream at the end of one hour, the amount of total proteins was elevated to 9.5 Gm. per hundred cubic centimeters, with the ratio of albumin to globulin 2.2 to 7.3, there was 12.4 to 13.7 mg. of calcium per hundred cubic centimeters, with 3.5 mg. to 4.5 mg. of phosphorus per hundred cubic centimeters, the uric acid amounted to 10 mg. per hundred cubic centimeters. There was severe secondary anemia.

The history of the past five years revealed that the patient had been treated at two other hospitals for an infectious arthritis of unknown origin. Low grade fever had been present almost constantly.

This case again illustrates the atypical nature of myeloma, with emphasis on arthritis as the clinical picture. The five year duration is noteworthy of the slow tempo of the disease process.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1938 TO JULY 1939

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Scrutiny of this year's literature on the activity and disturbances of the alimentary tract reveals, as usual, material of purely physiologic interest, observations based on clinical investigation and actual studies of disease in relation to diagnosis or therapeutics. No attempt will be made to review the entire literature on gastroenterologic subjects, as it is too voluminous and many of the contributions are merely repetitive. Articles have been chosen with a view chiefly to their clinical application. Many important articles dealing with nutritional problems that bear on the function of the digestive tract have been considered outside the scope of this review.

ESOPHAGUS

Little new has been added to knowledge of the physiology or of the diseases of the esophagus. It is important, however, to note the continued interest in the surgical treatment of carcinoma of the esophagus, inasmuch as palliative treatment by irradiation or bougienage is for the most part extremely unsatisfactory. Since Torek's successful resection of the thoracic portion of the esophagus for cancer in 1913, 31 additional cases have been reported, and, of these, 18 during the past three years. Adams and his co-workers¹ attacked the problem experimentally and attempted to develop a surgical method consistent with a reasonable prospect of success. Resection of as much as 4 inches (10 cm) of the thoracic portion of the esophagus with gastroesophagostomy was successfully performed in more than half of 13 experimental animals. This degree of success encouraged the authors to attempt a similar procedure in a patient with carcinoma of the thoracic portion of the esophagus. The operation was successfully performed, and the patient's convalescence was entirely uneventful. Such results are important in that they may eventually lead to a relatively safe standardized procedure that may be applied to what is usually considered an inoperable condition.

1 Adams, W. E., Escudero Bueno, L., Aronsohn, H. G., and Shaw, M. M. Resection of Thoracic Esophagus. Clinical and Experimental Study, *J. Thoracic Surg.* 7: 605, 1938.

A rather unusual esophageal obstruction reported by Waltz² was due to ingestion of a hygroscopic gum laxative ("saraka") One diachm (38 cc) of the preparation was swallowed by the patient, and immediately afterward a second diachm was taken with only a small amount of water Following the swallowing of the hygroscopic laxative, symptoms of esophageal distention and obstruction developed rapidly and were not relieved until the material was aspirated through an esophagoscope

Seven cases of peptic ulcer of the esophagus are reported by Chamberlin³ in an article in which the literature on the subject is summarized in a satisfactory fashion and the cause of the condition considered from a new angle, namely, the presence of a short esophagus or of a diaphragmatic hernia or of both Previous authors dealing with the subject have laid particular stress on the presence of an aberrant gastric mucosa in the lower third of the esophagus, but none has mentioned the aforementioned conditions as contributing to the formation of an esophageal peptic ulcer Chamberlin reports the results of both roentgenologic and esophagoscopic examinations, and in 6 of the 7 reported cases one or both of these abnormalities—a diaphragmatic hernia or a short esophagus—were present It is of interest that Jackson, who has reported more cases of peptic ulcer of the esophagus than any other observer, made no report of the roentgen findings in his cases While the subject is not new, the article is worthy of careful reading

STOMACH

The entire subject of the physiologic control of gastric acidity has been approached by numerous investigators, and a little further knowledge has been added This phase of gastric physiology is influenced by numerous factors, and studies regarding it are obviously of importance Several of the immediate variables in the complicated physiology of the gastric juice have been enumerated by Hollander⁴ and by Wilhelmj and Finegan⁵ Hollander mentions six factors of importance admixture of saliva, regurgitation of intestinal contents, peptic secretion, secretion of a specific dilution factor, mucus secretion and reabsorption

2 Waltz, M R Esophageal Obstruction Resulting from an Injudicious Method of Ingesting a Hygroscopic Gum Laxative (Saraka) Esophagoscopic Removal, *J A M A* **112** 229 (Jan 21) 1939

3 Chamberlin, D T Peptic Ulcer of the Oesophagus, *Am J Digest Dis* **5** 725, 1939

4 Hollander, F Factors Which Reduce Gastric Acidity, *Am J Digest Dis* **5** 364, 1938

5 Wilhelmj, C M, and Finegan, R W The Gastric Secretory Curve Before and After the Mann-Williamson Operation, and Its Bearing on the Normal Regulation of Gastric Acidity *Am J Digest Dis* **5** 373 1938

of hydrochloric acid All of these must be considered in any attempt to evaluate the gastric secretory mechanism

Factors Affecting Gastric Secretion—Certain factors, many of which importantly affect gastric secretion, have been studied carefully Schiff and associates⁶ observed the effect of intramuscular injections of theelin (an estrogenic substance) and conclude in their report that even over long periods of time this substance has little or no effect on gastric acidity Felson and Schiff⁷ studied the effect on gastric secretion of the subcutaneous administration of the gonadotropic substance from the urine of pregnant women (antuitrin-S) in 7 persons Daily doses of 1 cc of the substance were given for a total of from 32 to 150 injections No constant effects on the volume or the acidity of the gastric juice were noted

The effect of acetylbetamethylcholine hydrochloride (mecholyl) was studied by Flexner and Wright⁸ because of previous divergent reports following the use of this cholinergic drug Rabbits and cats showed little or no change in the gastric acidity following the subcutaneous injection of mecholyl Most human beings when proper care was taken to prevent swallowing of saliva showed a slight to marked rise in free and in total acidity following such an injection There was an associated marked increase in the flow of saliva, which became mucinous and more alkaline

The effect of continuous removal of gastric contents with resulting hypochloremia and alkalosis was studied by Lyall and Nicol⁹ Observations made on the gastric secretion under control conditions and during the conditions of the experiment revealed no significant changes in the composition of the gastric juice, even in the presence of marked changes in the chemical composition of the blood There was some diminution in the total volume of gastric juice secreted

A secretory depressant in the gastric juice itself has been reported by Brunschwig, Prohaska, Clarke and Kandel¹⁰ Their conclusions were reached during observations on the effect of intravenous injections of neutralized gastric juice in dogs The intravenous injection of their own

6 Schiff, L, Felson, H, Graff, J, and Meyer, B Effect of Estrogenic Hormone on Gastric Acidity, *Am J Digest Dis* 5 292, 1938

7 Felson, H, and Schiff, L The Effect of Anterior Pituitary-like Hormone on Gastric Acidity in Man, *Am J Digest Dis* 5 777, 1939

8 Flexner, J, and Wright, I S Effect of Acetyl-B-Methyl-Choline (Mecholyl) on the Gastric Secretion in Animals and in Man, *Am J Digest Dis* 5 736, 1939

9 Lyall, A, and Nicol, B M The Gastric Secretions in Experimental Hypochloreaemia, *J Physiol* 96 21, 1939

10 Brunschwig, A, Prohaska, J V, Clarke, T H, and Kandel, E A Secretory Depressant in Gastric Juice, read before the Central Society for Clinical Research, Nov 4, 1938

gastric juice or of that obtained from other animals produced no effect on gastric secretion. On the other hand, gastric juice obtained from patients with pernicious anemia and similarly treated produced in 9 animals out of 12 periods of achlorhydria. Similar material obtained from patients with cancer of the stomach resulted in temporary achlorhydria in 3 animals out of 6, whereas only 3 specimens obtained from patients with neither pernicious anemia nor cancer had any such effect. Boiling the "positive" juices for ten minutes destroyed the secretory depressant factor.

Day and Komarov¹¹ studied the effects of dextrose on the secretion of gastric juice in dogs. As found by previous investigators, the administration of hypertonic dextrose solutions (20 to 40 per cent) by the intravenous or intraduodenal route readily inhibited the gastric secretion provoked by sham feeding. Only a very concentrated solution (40 per cent) produced any appreciable inhibition of the secretion of the gastric juice evoked by rhythmic electrical stimulation of the vagi. Similarly, only moderate effects were noted on the secretion induced by the subcutaneous or intraduodenal administration of histamine, either with or without anesthetics. The authors advance the theory that the inhibitory effect of concentrated dextrose may be partly of central and partly of peripheral origin, in the latter case it is largely, if not entirely, due to changes in the osmotic condition of the body fluids.

Studies of gastric acidity in diabetic patients were carried out by Fenz¹² in a series of 116 patients. Anacidity (with a caffeine test meal) was found in practically half the patients and low acid content in about one sixth. Anacidity was more frequently found in untreated patients than in those receiving insulin and therefore could not be attributed to insulinization. The severity of the diabetes did not appear to determine the presence of anacidity, but it was noted that those patients who responded most readily to the administration of insulin were more apt to show anacidity. Of some interest is the finding that 44 of the 116 diabetic patients presented diarrhea, and of this group 70 per cent showed no free acid in the gastric contents. Of those with the most severe diarrhea, 80 per cent showed anacidity. The authors are inclined to believe that the diarrhea frequently noted in diabetic persons is most frequently gastrogenic in origin, although such a conclusion is open to some question.

An important and interesting study on gastric secretion was carried out by Seymour, Spies and Payne¹³ in 40 persons with chronic

11 Day, J. J., and Komarov, S. A. Glucose and Gastric Secretion, *Am. J. Digest. Dis.* **6** 169, 1939.

12 Fenz, E. Ueber die Anacidität der Diabetiker, *Wien. Arch. f. inn. Med.* **32** 283, 1938.

13 Seymour, W. B., Spies, T. D., and Payne, W. Gastric Secretion in Chronic Alcoholic Addiction, *J. Clin. Investigation* **18** 15, 1939.

alcoholism The volume of the gastric contents during fasting was 20 cc or less in over 70 per cent of the subjects, and the consistency was noted as being very thick and ropy Twenty minutes after the injection of histamine half of the subjects showed more than 20 cc of limp, clear gastric juice Only 2 out of the entire group had free acid during fasting, but this varied after repeated injections of histamine, some of the subjects tending to show free acid after several injections had been given Only 3 patients showed absence of pepsin from the gastric juice, and only 7 showed no rennin The findings are definitely suggestive of the effect of prolonged use of alcohol on gastric secretion, inasmuch as the achlorhydria persisted even after discontinuance of the use of alcohol for an appreciable period of time in 13 patients It should be noted that the duration of addiction was from seven to forty years In this particular group it is striking that the subjects were singularly free from gastrointestinal complaints and presented no evidence of a deficiency disease In addition to the foregoing observations, the authors show that the incidence of achlorhydria is even higher in persons with alcoholism who suffer from polyneuritis than in those with uncomplicated alcoholism

Necheles and his group¹⁴ undertook studies on gastric secretion in the presence of extragastric malignant tumor Sixteen rabbits with Brown-Pearce tumors were studied in an attempt to substantiate the clinical observation that human beings with extragastric malignant tumors have diminished gastric acidity No alteration in gastric acidity or pepsin was observed even in animals with extensive carcinoma These findings, together with the observation that diminished gastric acidity may be present long before the appearance of the malignant tumor, and the fact that a higher incidence of achlorhydria and diminished gastric acidity occurs normally with advancing years lead the authors to believe that a reduction in acid secretion in the stomach in cases of extragastric malignant tumor has not been satisfactorily established

The relationship between achlorhydria and the level of ascorbic acid in the blood has been studied by Alt, Chinn and Farmer¹⁵ Determinations of ascorbic acid were made in 44 cases of achlorhydria associated with pernicious anemia or iron deficiency With diets adequate in vitamin C, the plasma levels remained significantly below normal in patients with pernicious anemia but not in the iron deficiency group With diets inadequate in vitamin C, the plasma values decreased in both groups to well below the normal control levels The cause of this

14 Necheles, H, Appel, M, Wald, D, and Olson, W Gastric Secretion in Extragastric Malignancy, *Am J Digest Dis* 6 261, 1939

15 Alt, H L, Chinn, H, and Farmer, C J Blood Plasma Ascorbic Acid in Patients with Achlorhydria (Pernicious Anemia and Iron Deficiency Anemia), *Am J M Sc* 197 229, 1939

apparent variation in behavior between patients with pernicious anemia and those with iron deficiency anemia is not immediately obvious, but the mucosal changes characteristic of pernicious anemia with the associated changes in intestinal absorption may account for the differences observed

The relationship of gastric motility to anorexia was studied by Gulliksen and collaborators¹⁶ Of 200 children studied, 13 had a very low intake of food with moderately or definitely poor appetites Records of the hunger contractions in this group of undernourished, anorectic children showed that they had a greater number of contractions and a shorter interval between periods of activity and that the hunger contractions were less vigorous in height and duration than those observed in children with hearty appetites The authors suggest that the small appetites in such children may be due to lack of normal sensations of hunger

Beyer and Meek,¹⁷ in experiments on human beings, confirm the previous observations that benzedrine sulfate decreases the initial emptying time of the stomach but increases the period of final emptying The experiments indicate that the decrease in initial emptying time is due to a primary increase in tonus and activity of the stomach, raising intragastric pressure and forcing the contents through a pylorus the tonus of which, if altered by the drug, may be only slightly increased The delay in the final emptying is due to secondary inhibition of the gastric musculature with an increase in pyloric tonus The results suggest that whatever value benzedrine sulfate has in overcoming functional pylorospasm of a moderate degree is due to the initial stimulation of the gastric musculature, which overcomes the pyloric resistance, rather than to any direct inhibiting effect on the tonus of the pylorus

Effects of Smoking—Several articles on the effect of tobacco smoking on the physiology of the alimentary tract are of interest An article by Schnedorf and Ivy,¹⁸ although containing no new material, offers a good summary of previously described experiments and an excellent commentary Schnedorf and Ivy noted the effects of smoking on salivary secretion in 15 chronic smokers and 5 nonsmokers They observed the effects on the emptying time and the acidity of the gastric contents in 7 smokers without organic disease and in 22 smokers suffer-

16 Gulliksen, D. P., Fogelberg, A., and Kardos, L. Anorexia and Gastric Motility, *Am J Digest Dis* **5** 814, 1939

17 Beyer, K. H., and Meek, W. J. Effect of Benzedrine Sulfate on Gastric Emptying and Intestinal Activity, *Arch Int Med* **63** 752 (April) 1939

18 Schnedorf, J. G., and Ivy, A. C. The Effect of Tobacco Smoking on the Alimentary Tract. Experimental Study of Man and Animals, *J A M A* **112**: 898 (March 11) 1939

ing from peptic ulcer. Smoking reflexly stimulated salivary secretion in most of these subjects and inhibited hunger contractions of the stomach. It was found that when it has any effect on the stomach it tends to depress gastric secretion and retard evacuation. Only in occasional persons does it tend to cause significant changes in the gastric contents or an increase in gastric acidity. Incidentally, it tends to augment the motility of the colon but affects biliary and pancreatic secretion only when there are marked variations in the blood pressure. The authors conclude that only as a person approaches the limit of his tobacco tolerance do undesirable changes take place in the activity of the alimentary tract. All patients with peptic ulcer or with chronic disturbances who smoke should be cautioned regarding the undesirable effects of straining their tolerance to tobacco. Schnedorf and Ivy are unwilling to interpret any of their data as directly indicating that smoking has any beneficial effect on the digestive tract. Although they are quite properly cautious in the interpretation of their findings, a careful reading of their article is justified inasmuch as they contribute a rather timely and sound approach to the question of smoking in relation to digestive disturbances.

Two articles by Short and co-workers¹⁹ are also of interest. The first article represents an analysis of observations on 2,031 persons, of whom 1,292 were habitual smokers, in relation to symptoms referable to the respiratory, circulatory, gastrointestinal and nervous systems. In all of these systems the symptoms were increased among the smokers. The frequency of "heartburn" was increased by 100 per cent over that observed in the nonsmokers, and other digestive disturbances were noted to be increased in similar percentages. The statement that "the relation of tobacco smoking to gastric disturbances, especially hyperacidity, is a frequent clinical observation" is of interest in relation to their second article, which gives a direct comparison of the reaction of the human system to tobacco smoking and to epinephrine. Their observations confirm the view that the characteristic effects of tobacco smoking on the pulse, blood pressure, peripheral cutaneous temperature and blood sugar can be explained by an increased output of epinephrine, which is due most probably to the stimulative effect of nicotine on the sympathetic nerve-epinephrine system. The authors might have added that "heartburn" and so-called hyperacidity could also be explained properly by overstimulation of the sympathetic nerve fibers controlling the lower end of the esophagus.

19 Short, J. J., Johnson, H. J., and Ley, H. A. Effects of Tobacco Smoking on Health. Study of 2,031 Medical Records, *J. Lab. & Clin. Med.* **24**: 586, 1939.
Short, J. J., and Johnson, H. J. Direct Comparison of Reactions of Human System to Tobacco Smoke and Adrenalin, *ibid.* **24**: 59, 1939.

Peptic Ulcer—The etiologic nature of this chronic disease is still undetermined, although studies regarding the effect of lesions of the brain, alterations in hormonal activity and abnormal functioning of the autonomic nervous system continue to be of interest. Further evidence that discrete intracranial lesions may be the cause of ulceration of the upper part of the digestive tract is found in observations made by Oppen and Zimmerman,²⁰ who obviously have been stimulated by the previous studies of Cushing. These authors showed erosions in the esophagus, stomach or duodenum in 21 cases of lesions of the brain. The changes in the brain were of various etiologic character and variously localized in the midbrain, interbrain and cortex. They feel that gastrointestinal lesions in cases of cortical and mesencephalic involvement are most probably mediated through the hypothalamic nuclei.

Gauss²¹ also presents an interesting analysis of 20 cases of gastrointestinal symptoms in association with intracranial disease. In his series no ulcerations of the digestive tract were demonstrated, but his comments as to the genesis of digestive symptoms in relation to intracranial disease are stimulating. He attempts to subdivide the symptoms in these cases into three groups. The first group, including the commonest symptoms, classified as dyspeptic, includes nausea, vomiting, abdominal distress and changes in appetite in association with tumor of the brain. A second group of symptoms, classified as paroxysmal, is associated with the sensory and motor disturbances common to epilepsy, migraine and syphilis. A third and small group is that of the true peptic ulcer syndrome, which may occur at times in association with a tumor or other expanding intracranial lesion. He emphasizes the obvious wisdom of considering the possibility of a lesion of the brain when there are otherwise unexplained persistent disturbances of appetite and abdominal distress (with or without nausea and vomiting) not related to the normal gastric cycle. He also makes the important point that digestive symptoms of central origin are mediated by way of the lower levels of the central nervous system and hence have no localizing value.

In view of the publicity in the lay press attached to the treatment of ulcer with an extract of the posterior lobe of the pituitary, reported by Metz and Lackey,²² it is important to comment on their work. Following a preliminary report in 1937, these authors present observations on 28 persons suffering from peptic ulcer. They report complete

20 Oppen, L., and Zimmerman, H. M. Ulcers of Digestive Tract in Association with Cerebral Lesions, *Yale J Biol & Med* **11** 49, 1938.

21 Gauss, H. Gastrointestinal Symptoms in Disease of the Brain, *J A M A* **112** 701 (Feb. 25) 1939.

22 Metz, M. H., and Lackey, R. W. Peptic Ulcer Treated by Posterior Pituitary Extract. Two Years' Experience, *Texas State J Med* **34** 214, 1938.

symptomatic relief in 24 of the patients within three weeks after the start of treatment with a fresh preparation of the posterior lobe of the pituitary, administered hypodermically, orally or intranasally. The last route was preferred. The authors refer to previous studies on the influence of hypophysial extract on gastric secretion and adhere to the hypothesis that many patients with peptic ulcer exhibit pituitary deficiency. This assumption is largely based on the fact that 15 of their patients had definite polyuria and nocturia and responded more or less satisfactorily to the treatment. That the administration of posterior pituitary extract produced only a temporary healing effect on the ulcer is obvious from their statement: "Recurrences of ulcer healed under pituitary administration are to be expected, since this therapeutic agent probably relieves temporarily a deficiency." It is still too early to evaluate the results of such medication, and one is forced to recall the fact that almost any striking method for the treatment of peptic ulcer has always been of transient benefit. At the present time it will be wise to regard this latest addition to the therapy of ulcer as an interesting attempt to correlate certain known clinical facts with the manifestations of a chronic disease.

In this connection another important study has come from Sandweiss and collaborators²³ on the relation of gonadotropic hormones to peptic ulcer. These authors find, as have others, that pregnancy appears to have a beneficial effect on the symptoms of ulcer, and an examination of the records of 70,130 pregnant women consecutively admitted to hospital showed that only 1 had peptic ulcer. A high incidence of endocrinopathies, they thought, was found in 30 women with ulcers. Observations seemed to show that the symptoms of peptic ulcer are aggravated during the menopause. In addition to these clinical observations, studies were made on animals, a continuation of work reported last year. Of 34 Mann-Williamson dogs which had received daily injections of varying doses of the gonadotropic substance found in the urine of pregnant women (antuitrin S) and which had died, 50 per cent had no ulcers and 20 per cent had ulcers in the process of healing. Seventy per cent of the animals were therefore benefited during these injections. Ninety-eight per cent of the control Mann-Williamson dogs died of jejunal ulcers. The average time of survival of the control Mann-Williamson dogs was fifty-eight days, and the average of those treated with the gonadotropic factor was over one hundred days. In an attempt to produce similar results in human beings, 18 patients with active symptoms of peptic ulcers proved to be present were treated with daily injections of from 2 to 5 cc of the same gonadotropic substance for a

23 Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A. Relation of Sex Hormones to Peptic Ulcer, *Am J Digest Dis* 6 6, 1939.

period of fourteen consecutive days. Fourteen of the patients were benefited, but with commendable caution Sandweiss limits his enthusiasm to the suggestion that "in the dosage used, Antutrin-S produces no more beneficial effects than other parenteral products." No effect on the free or total acid secretion was noted following daily subcutaneous injections of from 2 to 5 cc of the substance. A note at the end of the article is probably important, stating that "preliminary observations on 20 Mann-Williamson dogs indicate that (a) urine from normal individuals contains a 'protective factor' against Mann-Williamson ulcers, and (b) this 'protective factor' is definitely absent from the urine of patients with peptic ulcer." The significance of these findings is still not clear, but there is little doubt that further careful investigations on the effect of endocrine secretions on normal and pathologic gastric function will be of interest.

As in previous years, numerous isolated experiences are noted regarding the cure or relief of peptic ulcer following unusual procedures. One such article is that reported by Bagdasarov and co-workers²⁴. They repeatedly transfused whole blood from goats to 82 patients with ulcers. The transfusions were performed at intervals of two to four days at first and subsequently at five to seven day intervals, 3 to 12 cc of blood being employed. Severe reactions were present in 8 per cent, and mild reactions were noted in nearly all patients so treated. Reactions typical of immediate and delayed allergic responses were not infrequently alarming. In spite of these reactions to transfusions of heterogenous blood, no fatalities were noted, and cures are claimed in about half of the cases followed. Although the findings are not without interest, one can hardly feel any enthusiasm about the method, especially as the authors point out seven absolute contraindications and three relative contraindications to its use.

Another new method for the treatment of ulcer is that described by Okada and Doi²⁵. These workers obtained extracts from the mucosa of the stomach and duodenum that are said to contain all the essential parts of each mucosa and to have a regenerating effect specific for the mucosa of each of the portions, respectively, of the digestive tract. Preparations of these extracts were administered intravenously in 60 cases, a full course of treatment consisting of thirty injections. The vast majority of both patients with ulcer and patients with other gastric troubles treated with either gastric or duodenal extracts were "cured or showed improvement, and the authors claim that the late results were

24 Bagdasarov, A. A., German, K. A., Gutson, G. I., and Zubelevich, M. M. Heterotransfusion du sang dans le traitement de l'ulcère gastro-duodénal, *Acta-med. U. R. S. S.* 1:497, 1938.

25 Okada, S., and Doi, T. Sur une nouvelle méthode de traitement de l'ulcère de l'estomac et du duodénum, *Arch. d. mal. de l'app. digestif* 28:935, 1938.

favorable The results suggest those obtained by the use of histamine and should be subject to the same objections Because of the frequency of favorable results from any parenteral treatment, one is inclined to be skeptical of the specific value of the aforementioned treatment and to recall the fact that in most instances an uncomplicated ulcer heals readily with any form of treatment within thirty days

The majority of articles dealing with the treatment of patients with peptic ulcer are concerned with various modifications of already well established medical or surgical procedures Of modifications in medical therapy, the majority, as usual, are concerned with measures directed toward reducing gastric acidity By far the greatest attention has been paid to the use of colloidal aluminum hydroxide Emery and Rutherford,²⁶ for example, like most writers, have found that symptoms of ulcer appear to be readily relieved by the administration of this substance, without any interference with the acid-base balance They think that there may be some slight absorption from the gastrointestinal tract but feel that this preparation avoids all danger of producing alkalosis They at first employed the continuous drip method of Woldman, but subsequently found that in most instances the oral administration of the drug was efficacious, an important point inasmuch as it simplifies the entire procedure for the average patient It is quite probable that the drip method of treating ulcer is applicable only to those patients who fail to respond to other measures, and these authors' experiences are similar to those of almost all observers

The beneficial effect of aluminum hydroxide gel appears to depend almost entirely on its action on gastric acid Quigley, Einsel and Meschan²⁷ administered massive doses of the preparation to dogs for seventy-nine days without any significant effect on the time of gastric evacuation or on the histologic structure of gastric tissue, and the gastric secretory response to histamine was only transiently reduced Ordinary amounts failed to produce any significant change in the motility or tone of the stomach or pyloric antrum The authors believe that in human beings the reaction is similar but that in the presence of ulcer or other pathologic changes in the stomach the preparation might have additional effects on gastric evacuation and secretory activity

Fauley, Ivy and collaborators²⁸ were unable to demonstrate on the basis of animal experimentation any prophylactic value of aluminum

26 Emery, E S, Jr, and Rutherford, R B Studies on the Use of Aluminum Hydroxide Gel in the Treatment of Peptic Ulcer, *Am J Digest Dis* **5** 486, 1938

27 Quigley, J P, Einsel, I H and Meschan, I Some Effects Produced in the Normal Stomach by the Ingestion of Moderate and Massive Quantities of Aluminum Hydroxide Gel, *J Lab & Clin Med* **24** 485, 1939

28 Fauley, G B, Ivy, A C, Terry, L, and Bradley, W B An Attempt to Prevent Postoperative Jejunal Ulcer by Aluminum Hydroxide Therapy An Experimental Study in Mann-Williamson Dogs, *Am J Digest Dis* **5** 792, 1939

hydroxide in the prevention of jejunal ulcers in Mann-Williamson dogs. In spite of the fact that large doses and a large series of animals were used, there was no evidence that the administration of aluminum hydroxide prevented the occurrence of jejunal ulcers. As a matter of fact, the authors expressed the belief that the medication caused a decrease in appetite with a resultant diminution in food intake and a more rapid loss of weight. They suggest that its use be avoided in patients suffering from peptic ulcer complicated by a relative pancreatic and biliary insufficiency or a gastroenterostomy.

Reports on the control of gastric acidity by magnesium trisilicate continue to appear, typical reports being those of Reid²⁹ and Tidmarsh and Baxter³⁰. The latter authors found that the addition of atropine and phenobarbital to magnesium trisilicate was of therapeutic value in that it brought about more restful nights, less apprehension and normal intestinal function.

The entire question of antacid therapy as related to peptic ulcer has been reviewed in an excellent article by Adams³¹. His review of the subject discloses nothing new but brings the entire matter up to date and presents it critically. There is a consideration of twenty-four substances that are administered orally to combat gastric acidity in the treatment of ulcer, in addition to comments on the use of mucin and hydrogen peroxide. The advantages and disadvantages of using these various substances are discussed with due regard to the chemical or physical activity of each and any unpleasant symptoms that may follow its use. The details of the pharmacologic action of each are presented. From the entire list Adams chooses colloidal aluminum hydroxide as the most appropriate medicament available at the present time for the control of gastric acidity.

An article by Eisele³² on changes in the acid-base balance during alkali treatment for peptic ulcer also presents nothing new but is more or less clarifying as far as a complete summary of the various occurrences associated with alkaline therapy is concerned. He points out succinctly the facts pertinent to the use of alkali, namely, that an occasional patient may sustain injury to the kidneys from alkali therapy.

29 Reid, C. G. The Control of Gastric Hyperacidity by Magnesium Trisilicate, *Am J Digest Dis* **6** 267, 1939.

30 Tidmarsh, C. J., and Baxter, R. G. Magnesium Trisilicate in Treatment of Peptic Ulcer, *Canad M A J* **39** 358, 1938.

31 Adams, W. L. A Critical Evaluation of Gastric Antacids, *Arch Int Med* **63** 1030 (June) 1939.

32 Eisele, C. W. Changes in the Acid-Base Balance During Alkali Treatment for Peptic Ulcer. Clinical Analysis of Alkalosis in Twenty-Eight Patients, *Arch Int Med* **63** 1048 (June) 1939.

and that almost certainly a preexisting renal disease will be aggravated by this form of treatment. He shows that during the treatment with alkalis the work of the kidneys is greatly increased. In effect, he presents a good argument for the use of other forms of antacid.

A very timely and pertinent short article is that of Hollander³³ on effective neutralization of gastric contents. In a few lines Hollander presents more clearly than is usually done the important considerations in regard to antacid therapy. He points out that the important consideration is the influence of the p_H of gastric juice on peptic activity. For the neutralization of free acidity a terminal p_H of about 3 or 3.5 is generally accepted, although complete neutralization of gastric acidity requires elevation of the p_H to at least 7. Hollander calls attention to the fact that the "acid-pepsin" factor is the major one in the genesis of peptic ulcer and that an effective reduction in gastric acidity minimizes the influence of this factor. For this purpose, however, the attention must be focused on acidity in relation to pepsin activity rather than solely on the figures for acid dilution. Peptic activity practically ceases at a p_H of 4.5 to 5. Complete neutralization of all organic acids is not necessary, nor does it offer any additional benefits, and Hollander suggests that, in contradistinction to the free acidity end point and the total acidity end point as a critical value in antacid therapy, there be introduced the proteolytic neutralization point, i. e., the p_H at which digestion of protein in the stomach is reduced to a minimum.

A statistical study of a large number of analyses of gastric content (2,877) is of some interest in this connection. The greater part of the article is given to a discussion of the significance of gastric acidity after stimulation by histamine with comments on the wide variation in values. One of the conclusions of the authors (Ruffin and Dick³⁴) is probably an important one in regard to the diagnostic value of gastric analysis. They state that if free hydrochloric acid is present after stimulation with histamine, the actual level of acidity is of little, if any, diagnostic significance. In other words, the authors by inference suggest that much of the diagnostic value of gastric analysis has been overemphasized. They also point out that the range of gastric acidity after histamine stimulation in normal persons is so great that it is impossible to determine what values are to be taken as evidence of normal acidity, hyperacidity or hypoacidity. In this series the incidence of achlorhydria

33 Hollander, F. What Constitutes Effective Neutralization of Gastric Contents? *Am J Digest Dis* 6:127, 1939.

34 Ruffin, J. M., and Dick, M. The Significance of Gastric Acidity After Histamine Stimulation. A Statistical Study of 2,877 Gastric Analyses, *Ann Int Med* 12:1940, 1939.

in normal controls compares closely with the findings of others. A particularly interesting finding is that 24 patients (54 per cent of the series) with active duodenal ulcers, as shown by x-ray pictures, had no free acid after stimulation with histamine.

A series of reports have appeared relating to the level of ascorbic acid in the blood of patients with peptic ulcer. No new facts have been presented, however, following the original finding that, along with other conditions that are associated with a limitation of diet the plasma values for vitamin C are low. Some interest attaches to the report by Warren, Pijoan and Emery,³⁵ which summarizes studies of vitamin C saturation in a small group of patients with active duodenal ulcer. It was found that these patients utilized 20 per cent more ascorbic acid than do normal persons. There was no evidence that they were unable to absorb the drug when it was given by mouth. These authors point out an important fact that the usual Sippy diet contains much less than the normal requirement of vitamin C, but they do not feel that evidence exists at present that vitamin C therapy has any direct healing influence on ulcer.

The use of pectin as prophylactic and curative of experimental ulcers in animals was studied by Winters, Peters and Crook.³⁶ A control group of dogs were treated with cinchophen, and typical ulcers were produced in each instance. Of 9 dogs similarly treated except for the addition of pectin to their diet, 8 did not acquire ulcers. Two animals which were proved by operation to have cinchophen ulcers were subsequently treated with both cinchophen and pectin. These animals were put to death on the twenty-first and twenty-fifth days, respectively, after operation, and postmortem examinations showed well healed ulcers. Further reports as to the value of pectin in the therapy of ulcer, especially in human beings, are needed in determining whether this preparation constitutes an addition to the present armamentarium for the treatment of ulcer.

The appearance of a large number of articles on the treatment of bleeding ulcer is evidence of a renewed interest in the optimum treatment for the patient suffering from a massive hemorrhage. There is a wide divergence of opinion as to the details of therapeutic measures, but there can be little doubt that the experience of most observers warrants the assumption that such patients should be treated by medical measures except on rare occasions. There is general agreement as to

35 Warren, H. A., Pijoan, M., and Emery, E. S., Jr. Ascorbic Acid Requirements in Patients with Peptic Ulcer, *New England J. Med.* **220** 1061, 1939.

36 Winters, M., Peters, G. A., and Crook, G. W. Pectin as a Prophylactic and Curative Agent for Peptic Ulcers Produced Experimentally with Cinchophen, *Am. J. Digest. Dis.* **6** 12, 1939.

the fact that massive hemorrhage from an ulcer involves relatively slight risk when the patient is under the age of 45 years, and the vast majority of observations lead one to the conclusion that the policy of withholding food from a patient with a bleeding ulcer is definitely unwise. Various modifications of Meulengracht's liberal dietary regimen are reported, but the fundamental principles of small frequent feedings of simple food instituted without delay after a massive hemorrhage seems to be agreed on with few exceptions. It is probable that the details of the dietary regimen in such an emergency are of relatively minor importance. There is rarely a patient in the younger group and a slightly larger percentage of the patients over the age of 45 years for whom surgical measures must be considered. The danger of a gastric surgical operation in the presence of massive hemorrhage is so great, however, that the decision to operate should be reached only after a careful consideration of the patient's case by both the physician and the surgeon. When surgical measures are indicated, they should not be delayed beyond forty-eight hours after the original hemorrhage. An excellent discussion of the surgical aspects of the problem is presented by Pfeiffer,³⁷ and a clear exposition of the difficulties in deciding on such an emergency operation is added by Miller and Elsom³⁸ from the point of view of the internist.

Statistics on the actual mortality from bleeding ulcer still leave much to be desired. Hesser³⁹ reports an interesting series which includes 122 cases of ulcer with 2 or more hemorrhages. In this group of cases of ulcer with recurrent hemorrhages there were only 4 deaths, 3 of which occurred in patients over the age of 60. Herlihy⁴⁰ presents a report of twelve months' experience with Witts' modification of Meulengracht's routine. No patients were operated on, and there was a mortality of 4 per cent. He stresses the important point of not handing the surgeon a "foiled hope."

An important article is that of LaDue,⁴¹ as it refers back to the original work of Lenhartz, in 1906, who gave an egg albumin and milk diet immediately after hemorrhage in 146 cases, with a mortality of 2.14 per cent. LaDue's work properly gives credit to Andresen,

37 Pfeiffer, D. B. Gastric Hemorrhage, *J. A. M. A.* **111** 2198 (Dec. 10) 1938.

38 Miller, T. G., and Elsom, K. A. The Management of Massive Hemorrhage from Peptic Ulcer, *M. Clin. North America* **22** 1711, 1938.

39 Hesser, S. Relapsing Gastric Hemorrhages and Their Treatment, *Acta med. Scandinav.* **98** 340, 1939.

40 Herlihy, J. D. Immediate Feeding in Hematemesis and Melena, *M. J. Australia* **2** 996, 1938.

41 LaDue, J. S. Treatment of Massive Hemorrhage Due to Peptic Ulcer, *Arch. Int. Med.* **63** 1017 (June) 1939.

whose report in 1927 of the treatment of bleeding ulcer by dietary measures should have received much more attention than it has. Andersen's methods have been carried out by LaDue, who states that in principle they correspond to those subsequently introduced by Meulengracht. Transfusion by the gravity drip method is accepted by most authors as a valuable and important adjunct to the treatment of patients with bleeding ulcer.^{*} It is rather surprising to note, however, that in LaDue's report, based on Andersen's teaching, transfusion and the intravenous administration of fluids are considered to be contraindicated. This is not in accordance with the experience of most writers, who are convinced that drip transfusion does not cause any appreciable rise in blood pressure and is beneficial rather than otherwise.

Browne and McHardy⁴² report on 131 patients with bleeding ulcers, showing a mortality in those treated medically of 3.4 per cent. They do not advocate the immediate institution of feeding after hemorrhage. They recommend the continuous aluminum hydroxide drip method suggested by Woldman as the treatment of choice during the first few days after hemorrhage. Crohn and Lerner⁴³ agree as to the value of conservative medical treatment for such patients but state that their experience with Meulengracht's diet has not been encouraging. They still prefer starvation during the early period of treatment.

Further experiences in the treatment of this frequent complication of ulcer are required before a complete evaluation of the details of medical management can be obtained, but the present indications are that some modification of the principle of frequent small feedings of simple food given immediately after hemorrhage has ceased will be found advisable. Whether the generous dietary permitted by Meulengracht is preferable to the more limited one advocated by Andersen, consisting essentially of gelatin and cereals, remains to be seen. At present many authors prefer the administration of vitamin C as an adjunct to the medical treatment of the patient with bleeding ulcer, but it is generally admitted that there is no satisfactory evidence as yet that this form of therapy is rational.

Attempts are still being made to study the retention of nitrogen and the high blood urea following massive gastrointestinal hemorrhage. Little new has been added to Christiansen's work, but a report by Borst⁴⁴ is of some interest. This author gives a detailed study of 3

42 Browne, D. C., and McHardy, G. Management of Peptic Ulcer Hemorrhage, *Am J Digest Dis* 6:87, 1939.

43 Crohn, B. B., and Lerner, H. H. Gross Hemorrhage as a Complication of Peptic Ulcer, *Am J Digest Dis* 6:15, 1939.

44 Borst, J. G. G. Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage from Peptic Ulcer, *Acta med Scandinav* 97:68, 1938.

patients with gross hemorrhage showing retention of nitrogen and chlorides in the blood and a low level of chlorides in the urine. The retention of nitrogen is attributed to an increased formation of urea from the blood in the intestinal tract. The concentration of urea in the urine remains high until the blood volume is restored. During posthemorrhagic dilution of the blood the kidneys excrete neither sodium nor chloride, with the result that if sodium chloride is given, the plasma chlorides rise markedly above normal, with excessive amounts of potassium being excreted in the urine. He advocates drip transfusions for the purpose of restoring red blood cells and plasma protein and the administration of fluids at the same time until the concentration of urea in the urine drops below maximum and the chloride content rises. He also advocates the determination of urea clearance as the best method of measuring the severity of the shock. Although the findings corroborate the results of previous studies and are of interest, it seems possible that too much therapeutic and prognostic importance has been assigned to this interesting phenomenon of nitrogen retention following gross hemorrhage. Clinical experience seems to suggest that simple determinations of red blood cells, hemoglobin and fluid balance plus close observation of the pulse and blood pressure are preferable and more reliable criteria for determining treatment and prognosis than these more complicated measures.

Black⁴⁵ corroborates the evidence for a lowering of urea clearance in this condition and states that in the 12 cases which he studied the urea clearance rose to normal within a week after the hemorrhage. He believes that there is some correlation between red cell volume and urea clearance and that his estimations indicate some degree of impairment of renal function, although present evidence is insufficient to establish definitely the mechanism of the renal impairment.

Dill and Isenborn⁴⁶ present observations as to the incidence and cause of fever in patients with bleeding peptic ulcer. Two hundred male patients who were proved to be suffering from peptic ulcer were studied, and 53 per cent were found to have a slight elevation of temperature (over 99 F). Of the group with bleeding ulcers, 80 per cent were febrile, whereas only 46 per cent of the patients with nonbleeding ulcers had an elevated temperature. In a group of patients without demonstrable organic disease, 37 per cent of the patients showed evidence of some elevation of temperature (1 e, 99 F or above for more than two days, 99.2 F or above for two days, or any single rise above 100 F). A comparison of these with the patients who had ulcer showed that the latter

45 Black, D. A. K. Urea Clearance in Hematemesis, *Lancet* **1** 323, 1939.

46 Dill, L. V., and Isenborn, C. E. Observations in Incidence and Cause of Fever in Patients with Bleeding Peptic Ulcers, *Am J Digest Dis* **5** 779, 1939.

presented an elevation of temperature more frequently than patients without demonstrable organic disease, a tendency increased by hemorrhage. Anemia, with or without evidences of gross hemorrhage, seems to increase the tendency toward a slight elevation of temperature. The conclusion reached by the authors that the absorption of blood degradation products plays little part in the production of fever seems rather unwarranted, however, in view of their own observations and those of others. Their suggestion that patients with gastric neuroses are relatively prone to slight elevations of temperature is of interest and is probably correct.

In view of the foregoing findings the report of Demole and Perret⁴⁷ regarding the speed of sedimentation of red cells in cases of gastroduodenal ulcer is of some interest. Using Westergren's technic, they studied 102 cases. There was a normal sedimentation rate in 80 per cent of the cases of simple uncomplicated gastroduodenal ulcer, the rate was accelerated in 63 per cent of the cases of ulcer complicated by stenosis, penetration or bleeding. A point of interest is that gross hemorrhage apparently does not cause immediate acceleration of the sedimentation rate. The authors obviously suggest that an elevated sedimentation rate should make one suspicious that complications have arisen in an otherwise simple ulcer.

The surgical treatment of peptic ulcer is still somewhat unsettled, the divergent points of view ranging from those of Finsterer and Berg to those of more conservative surgeons. It will be worth while to suggest the soundness of the point of view expressed by Cutler,⁴⁸ who comments on the type of operation to be employed in cases in which surgical intervention is indicated. In a review of the surgically treated patients at the Roosevelt Hospital between the years 1934 and 1937, the following guiding principles in the choice of operation have been evolved: (1) The operation must be of such a nature that the particular patient can tolerate and survive it, (2) not only should it aim at the alleviation of symptoms, but it should give freedom from the likelihood of complications, both early and late, (3) the ideal procedure having been determined, it should be abandoned at operation if the condition warrants it. One might add as a fourth desideratum that a final decision for or against surgical intervention should rest on a balancing of risks, namely, the risk of operation as opposed to the risk of a continuation of non-

47 Demole, M., and Perret, P. E. Notions statistiques sur la vitesse de sedimentation dans l'ulcere gastro-duodenal, *Arch. d. mal. de l'app. digestif* **29** 194, 1939.

48 Cutler, C. W., Jr. Changing Methods in Surgical Treatment of Peptic Ulcer. Study of Cases Operated upon at Roosevelt Hospital, New York. *Ann. Surg.* **108** 68, 1938.

surgical measures The type of surgical procedure to use in the treatment of peptic ulcer must always remain an individual decision in a given case

Most authors who are experienced in the treatment of peptic ulcer will be in general agreement with the conclusions expressed by Allen and Welch,⁴⁹ who point out the marked change in such therapy during the past twenty years Prompt surgical intervention is indicated for the patient in whom acute perforation develops and is occasionally required in an episode of massive bleeding Thorough medical care is indicated for all others Patients in whom cicatricial obstruction of the pylorus develops do well with gastroenterostomy, those in whom ulcers develop which are intractable to medical care or which have been associated with massive hemorrhage should receive subtotal gastrectomy That a gastroenterostomy is still the operation of choice in a few of the older "poor risk" patients is the opinion of most conservative physicians and surgeons, and in patients thus treated, even in the absence of obstruction, favorable results are usually obtained

As a commentary on the futility of ill advised surgical treatment, the report of Finsterer⁵⁰ is important He reviews his own surgical results in 331 patients (of 2,753) on whom previous operations had been performed for the relief of symptoms of ulcer Exclusive of operations for acute perforation, acute hemorrhage or gastrocolic fistula his mortality figure was 8.6 per cent The operation most frequently performed prior to that done by the author was gastroenterostomy (in 190 patients), with a subsequent failure of the original ulcer to heal or the formation of a jejunal ulcer Six and eight tenths per cent of those patients who previously had undergone gastroenterostomy died as a result of further surgical operation, whereas the mortality from an operation after a previous resection was 23.5 per cent Finsterer states that the occurrence of a jejunal ulcer after a radical resection of the stomach is always due to technical faults, an indication for extreme caution in advising this radical procedure

The necessity for special care of the "poor risk" patient is being more clearly recognized by physicians and surgeons alike When surgical treatment is indicated, the preoperative and postoperative nutrition may be of paramount importance in the reduction of mortality and the avoidance of postoperative complications, such as nutritional edema at the site of operation For this reason the closest collaboration between the physician and the surgeon is necessary for the production of optimum

49 Allen, A. W., and Welch, C. E. Peptic Ulcer Considered from a Surgical Point of View, *New England J. Med.* **220** 103, 1939

50 Finsterer, H. Results of Repeated Operations on the Stomach, *Surg., Gynec. & Obst.* **68** 334, 1939

results, a fact that is universally recognized by the most experienced surgeons. Attention has recently been directed toward this phase of the surgical management of ulcer by such men as Ravdin⁵¹ in this country.

In a discussion of recurrent peptic ulceration after gastric operation Kelly⁵² specifically emphasizes the importance of the avoidance of all kinds of rigid starvation before and after any operative procedure, and several methods of postoperative feeding are introduced. Of these, a jejunostomy accompanying or following the original operation or the introduction of a double lumen tube through the stoma into the jejunum at the time of operation, as advocated by Abbott and Rawson,⁵³ deserves serious consideration.

The parenteral administration of vitamins as an adjunct in these difficult cases has been stressed by various authors, and particular stress has been laid on the need for vitamin B complex and for vitamin C. A specific indication for the use of the latter preoperatively and postoperatively was originally suggested by the work of Lanman and Ingalls and has been further emphasized by the recent work of Bartlett, Jones and Ryan,⁵⁴ who show that apparently there is a striking need for ascorbic acid during the early period of wound healing immediately after operation.

The necessity for adequate amounts of protein in these patients is generally recognized, but so far the problem of supplying it has been only partially solved by the use of frequent blood transfusions. In this connection the work of Elman and Weiner⁵⁵ is of extreme interest and leads to the hope that eventually some preparation will be evolved which contains adequate amounts of nitrogenous material and which can be administered intravenously. These authors are the first to report the intravenous administration of a mixture of amino acids to human beings as a means of parenteral protein alimentation. The mixture was obtained by the addition of 2 per cent tryptophan and cystine to the product of acid hydrolysis of casein. No evidence of toxicity was observed if the injections were given slowly. The injected amino acids were rapidly

51 Ravdin, I. S., Stengel, A., Jr., and Regel, C. The Control of Hypoproteinemia in Surgical Patients, *J. A. M. A.*, to be published.

52 Kelley, R. E. Recurrent Peptic Ulceration. Causes of and Design for the Second Operation on the Stomach, *Lancet* **1** 1, 1939.

53 Abbott, W. O., and Rawson, A. J. A Tube for Use in the Postoperative Care of Gastro-Enterostomy Patients—A Correction, *J. A. M. A.* **112** 2414 (June 10) 1939.

54 Bartlett, M. K., Jones, C. M., and Ryan, A. E. Vitamin C Studies on Surgical Patients, *Ann. Surg.*, to be published.

55 Elman, R. and Weiner, D. O. Intravenous Alimentation, with Special Reference to Protein (Amino Acid) Metabolism, *J. A. M. A.* **112** 796 (March 4) 1939.

utilized, as was indicated experimentally and clinically by the nitrogen balance, the regeneration of serum protein and the reduction of nutritional edema. This mixture was administered to about 20 patients, but only 8 received large amounts for more than one or two days. The method is still too expensive for practical purposes, largely on account of the necessity for the addition of tryptophan, which is essential for the support of normal nitrogen metabolism, but the idea is sound, and the necessity for such a procedure will undoubtedly lead to more practical results.

Accurate knowledge of the postoperative appearance and function of the stomach after subtotal resection is still lacking, although roentgenologic and gastroscopic studies are gradually accumulating. The importance of these studies is obvious inasmuch as they undoubtedly help to explain the persistence of many troublesome symptoms after radical operations. One such study is that reported by Shekhter,⁵⁶ who made roentgen observations in 60 cases of subtotal resection for ulcer. Eleven cases were studied during the three months after gastric operation, and 10 cases were studied for periods of two, three and five years after operation. Careful observations were made on the inflammatory mucosal edema, with narrowing of the stoma and delay in gastric evacuation, which appeared shortly after resection. This edema disappeared in uncomplicated cases in the course of three months, leading to the type of evacuation characteristic for many given types of resection. The need for correlation of such observations with direct gastroscopic observations is obvious.

Cancer —Cancer of the stomach of necessity attracts a good deal of attention, but the means of making an early diagnosis of this condition still leave much to be desired. Hurst⁵⁷ has contributed an article on cancer of the alimentary tract that is rather interesting, particularly in its analysis of cancer statistics. Various social strata in England are studied and a comparison made with similar strata in Holland. Hurst brings his account of cancer of the stomach up to date and discusses its genesis in a general but interesting fashion. He quotes Cramer to the effect that the total incidence of cancer is approximately the same in all countries, all classes and both sexes but expresses the view that the incidence of cancer of the stomach shows a remarkable difference in different nations and classes. Thus cancer of the stomach accounts for only 22 per cent of deaths from cancer in males in England, compared with 45 per cent in Sweden and 55 per cent in Holland. It is twice as

56 Shekhter, I. A. Shape, Position and Motor Function of Stomach After Resection for Ulcer, *Novy khir. arkhiv* **41** 346, 1938.

57 Hurst, A. Cancer of the Alimentary Tract. Its Pathogenesis and Its Prophylaxis, *Lancet* **1** 533, 1939.

frequent in the lower social classes in England as among the well-to-do, whereas the incidence of carcinoma of the colon and rectum is the same in both classes. A comparison between the figures obtained from Guy's Hospital and other English general hospitals representing the English poor and those obtained from New Lodge Clinic, representing the well-to-do and from University Clinic of Amsterdam and Utrecht shows that in Holland the stomach is involved in 37 per cent of cases of cancer of the alimentary tract as compared with 63 per cent in England. In agreement with other authors he stresses the apparent importance of the excessive use of alcoholic beverages and tobacco in association with cancer of the esophagus. One important point in regard to cancer of the colon is Huist's impression that it is not found with any greater frequency in patients suffering from diverticulitis than in the general run of patients.

Another excellent presentation of this subject is that of Jordan⁵⁸ who reports on 251 cases, in 187 of which the carcinoma was considered operable. The age incidence, the localization of the cancer and the relation to achlorhydria are all discussed. She emphasizes the importance of periodic check-ups for patients who have achlorhydria, especially when it is known to be in association with healed gastric ulcer. Instead of accepting the usual defeatist attitude that is held by so many members of the medical profession, she makes a plea for "rugged individualism" in the treatment of cancer of the stomach, with disregard for the average discouraging prognosis of the disease. This attitude is warranted by the fact that in a series of approximately 100 cases in which the patient was followed after resection of a tumor the patient lived four years or more after operation in almost one seventh of the instances.

A point of some clinical interest is that raised by Rivers and Dry⁵⁹ in a discussion of pain in relation to cancer of the stomach. In a general way it can be said that patients with cancer of the stomach whose gastric secretion is normal or above are much more likely to experience pain than those who have achlorhydria or only a trivial amount of hydrochloric acid. Such a point is not unexpected but is worthy of mention.

An unusual case report of Phillips and Rivers⁶⁰ should be mentioned in which 2 carcinomas involved the stomach in the same patient, with an eleven year interval between them. The first tumor appeared when the

58 Jordan, S. M. Medical Aspect of Cancer of the Stomach, *J. A. M. A.* **112** 618 (Feb. 18) 1939.

59 Rivers, A. B., and Dry, T. J. Pain in Cancer of Stomach. Preliminary Report, *Am. J. Digest. Dis.* **5** 732, 1939.

60 Phillips, R. B., and Rivers, A. B. Two Carcinomas Involving the Same Stomach with an Eleven-Year Interval Between Them. *Am. J. Digest. Dis.* **6** 37, 1939.

patient was 22 years of age, was extremely malignant but was successfully removed, and the patient survived for eleven years, at which time he was operated on a second time, again for cancer of the stomach. If the second tumor represented a recurrence, the interval of freedom from symptoms is of interest. However, the fact that the histologic appearance of the second growth appeared definitely different from that removed at the first operation makes it probable that the second cancer arose independently of the first one.

A note by Dobbs⁶¹ on the treatment of pyloric stenosis with atropine methylnitrate (eumydrine) may be mentioned. A series of 20 infants with pyloric stenosis were treated with this drug, and 16 were apparently cured. Three were operated on successfully after atropine methylnitrate had failed to relieve vomiting. One infant died during treatment with the drug. The diagnosis of pyloric stenosis was based on a typical history, visible peristalsis and a palpable pyloric tumor. Dobbs points out that dehydration and alkalosis were relieved by the subcutaneous administration of physiologic solution of sodium chloride before the administration of the drug. Hypodermoclyses were used as long as the intake of fluids by mouth was insufficient.

Another article referable to pylorospasm is that of Wolfe,⁶² who reports 5 cases in which the condition simulated ruptured or perforated peptic ulcer. Prompted by the similarity between spasm of the digestive tract and bronchial spasm, the author conceived the idea of administering epinephrine as a diagnostic measure. Marked relief of the spasm of pain was observed in five to fifteen minutes in every instance. The author feels that in the presence of perforation epinephrine would have no effect and that therefore its use constitutes a diagnostic method of importance. The procedure is of interest, although one is inclined to believe that a careful physical examination would permit a correct diagnosis in most instances. The procedure is accompanied by no risk however and conceivably may be of real diagnostic value.

Gastroscopy—The latest addition to methods for the diagnosis of disease of the stomach, gastroscopy, has been thoroughly reviewed during the past year. Few, if any, new observations have been added to the large number made by Schindler, Benedict and numerous others. A comprehensive summary of the entire subject has been presented by Schindler,⁶³ which will be found authoritative by those interested in this extremely important subject.

61 Dobbs, R. H. The Treatment of Pyloric Stenosis with Eumydrin, *Lancet* **1** 12, 1939.

62 Wolfe, J. Hypodermic Use of Adrenalin for Differential Diagnosis Between Acute Pylorospasm and Ruptured Peptic Ulcer, *Virginia M. Monthly* **65** 405, 1938.

63 Schindler, R. Role of Gastroscopy in Recognition and Identification of Gastric Lesions. Collective Review, *Internat. Abstr. Surg.* **67** 443, 1938.

A technical modification of the flexible Wolfe-Schindler gastroscope has been devised by Jennings⁶⁴ It consists of an instrument with a magnetic control of the objectives The author claims that it gives a closer view of lesions of the lesser curvature and diminishes blind areas although it fails to give complete visualization of the antrum It is used in conjunction with a narrow angle gastroscope It is questionable whether this modification offers any real advantages over the instrument at present in almost universal use

Observations on the effect of acetylsalicylic acid and of certain other substances on the stomach are reported by Douthwaite and Lintott⁶⁵ They confirm the general impression that acetylsalicylic acid is a gastric irritant and apparently may produce submucous hemorrhages and chronic gastritis The calcium salt of acetylsalicylic acid seems to be the least irritating preparation available

Schindler⁶⁶ calls attention to the importance of localized gastric purpura as evidenced by mucosal hemorrhages and round accumulations of pigment, found most frequently about 3 cm above the angulus along the lesser curvature These absorb slowly, and the lesion may occasionally develop into a hemorrhagic erosion He suggests the possibility that such a hemorrhagic lesion may precede the occurrence of the acute stage of gastroduodenal ulceration He also presents⁶⁷ an excellent summary of gastroscopic observations made on 23 patients with pernicious anemia, 3 of whom were examined before and after adequate treatment and 14 of whom were observed only after intensive therapy All of the untreated patients showed superficial gastritis with atrophy, or patchy or diffuse atrophy After treatment 4 patients showed no improvement in the gastric mucosa, and an additional patient showed progression of gastric atrophy under adequate therapy Seven patients who had received proper treatment of the underlying condition showed a normal mucosa of the gastric antrum, while in another there was almost complete regeneration of the gastric mucosa In 4 patients all portions of the stomach appeared to be absolutely normal He explains these findings by assuming that in pernicious anemia there are two separate diseases of the stomach, he supposes that primarily there is a dysfunction of the mucosal cells which produce the antianemic factor

64 Jennings, D B M A Flexible Gastroscope with Magnetic Control of Objective, *Lancet* **1** 1153, 1939

65 Douthwaite, A H, and Lintott, G A M Gastroscopic Observation of Effect of Aspirin and Certain Other Substances on the Stomach, *Lancet* **2** 1222 1938

66 Schindler, R Chronic Localized Gastric Purpura, *Am J Digest Dis* **5** 796, 1939

67 Schindler, R, and Serby, A M Gastroscopic Observations in Pernicious Anemia, *Arch Int Med* **63** 334 (Feb) 1939

and that secondarily there is degeneration of the surface epithelium with superimposed gastritis, which may or may not heal when the deficiency state is eliminated. The secondary inflammation is usually associated with similar disturbances of the tongue and intestine, dysfunction of the hemopoietic apparatus and combined degeneration of the spinal cord. At times, he believes, one may see a severe but reversible atrophic gastritis without associated blood changes, and suggests that a new term be substituted for that of "antianemic factor." The article is more complete than any other previously published on the subject, and it confirms many of the previous findings.

Robertson⁶⁸ comments on the findings in cases of ulcerative gastritis in relation to residual lesions. He describes in detail the microscopic appearances of stomachs with healing or incompletely healed lesions and emphasizes the importance of frequency of superficial mucosal hemorrhages, citing Beaumont's original observations. He states that the hemorrhages that are due merely to overdistention of capillary loops are always followed by necrosis and subsequently by more or less healing. From these superficial lesions, deeper and more extensive ulcerations into the muscularis may occur, with distortion of the gastric architecture, and these are similar to the lesions produced experimentally with cinchophen. The residual (unhealed) lesions of "ulcerative gastritis" appear to be the most common lesions of the gastric wall. The author quite correctly objects to the use of the term "chronic gastritis" without modification.

Bank and Renshaw⁶⁹ present an interesting attempt to correlate observations of the secretory and motor functions with gastroscopic findings. In 50 patients with chronic superficial gastritis no characteristic secretion was noted. Hyperacidity was found in 50 per cent of the patients and anacidity in 25 per cent, these figures differing from those in other reports which have included all forms of gastritis. The authors claim that the incidence of anacidity is greater in this group of patients than in the group without gastrointestinal symptoms, but unfortunately they do not take into consideration the age distribution. Chronic superficial gastritis, according to Bank and Renshaw, is characterized by a delayed emptying time in more than half of the patients, and patients with achlorhydria and gastritis fail to show hypermotility. Sixty-five additional patients with gastroduodenal ulcerations were studied by means of the gastroscope to estimate the relationship between

68 Robertson, H. E. Ulcerative Gastritis and Residual Lesions, *J. A. M. A.* **112** 22 (Jan. 7) 1939.

69 Bank, J., and Renshaw, J. F. Chronic Superficial Gastritis. Correlation of Gastric Analysis and Clinical Study with Gastroscopic Examination, *J. A. M. A.* **112** 217 (Jan. 21) 1939.

gastritis and six hour retention as observed in roentgen examination. The conclusion was reached that gastritis is not dependent on retention.

An article by McNeer and Barowsky⁷⁰ based on more than 200 gastrosopic examinations of 143 patients contains certain points of importance. The authors show that the belief that true achylia is an expression of atrophy of the gastric mucosa is not supported by gastrosopic study. This, of course, is in agreement with numerous recorded observations on patients with pernicious anemia in remission. One observation, while not original, is important, namely, that gastritis may occasionally simulate a gastric neoplasm to such an extent that even gastrosopically it may be difficult to differentiate between the two. This is particularly true in occasional cases of diffuse scirrhous carcinoma.

SMALL INTESTINE

Aside from a consideration of duodenal ulcer the articles concerning this portion of the alimentary tract deal primarily with pathologic or anatomic abnormalities and for the most part are of only moderate interest. One article on the physiology of the small intestine is that of Althausen and Stockholm.⁷¹ These authors, who have been interested in the absorptive activity of the small bowel for some time, report on the influence of the thyroid gland on absorption in the digestive tract. Administration of a thyroid extract to rats markedly increased the absorption of dextrose, galactose, xylose and oleic acid but did not affect the absorption of alanine. Thyroidectomy caused considerable reduction in the absorption of dextrose, and the absorption of xylose in rats treated with thyroxin was increased, apparently by abnormally rapid emptying of the stomach. The absorption of dextrose, galactose and oleic acid was increased with thyroxin treatment, probably because of a stimulation of the mechanism of phosphorylation. This increased absorption of dextrose appears to take place chiefly in the small intestine. Althausen's findings indicate that the thyroid hormone influences intestinal absorption mainly by increasing phosphorylation and by stimulating gastric emptying. The discovery that thyroxin specifically stimulates the absorption of substances susceptible of phosphorylation and that phlorhizin inhibits this stimulating action confirms Verzar's theory of selective intestinal absorption through phosphorylation. Clinically, altered absorption is an important factor in the production of abnormally high sugar tolerance curves in patients with hyperthyroidism and unusually low sugar tolerance curves in patients with myxedema.

70 McNeer, G., and Barowsky, H. A Gastrosopic Study of the Incidence of Chronic Gastritis in Common Gastric Afflictions, *Am J Digest Dis* **6** 180, 1939.

71 Althausen, T. L., and Stockholm, M. Influence of the Thyroid Gland on Absorption in the Digestive Tract, *Am J Physiol* **123** 577, 1938.

A report by Lieber, Stewart and Lund⁷² contains a good statistical study of 222 cases of carcinoma of the prepapillary portion of the duodenum, and includes 17 of their own cases. It should be pointed out that inadequate roentgen studies seem to have been made in the vast majority of cases, which may explain the fact that in only 17 per cent of the cases was the condition correctly diagnosed previous to operation. The mortality following operative treatment of the condition is extremely high, representing 50 per cent of the 122 cases that came to surgical attention. There was 78 per cent mortality among 51 patients subjected only to palliative surgical treatment for obstructive jaundice, whereas of 57 patients who had the primary growth resected, only one third died. Jaundice occurred in practically all of these patients, pain in about two thirds and fever in one third. A palpable mass was noted in only 4 patients, although the liver was palpable in three fourths of the patients and the gallbladder in one half.

Foshee and McBride⁷³ report a case of leiomyosarcoma of the duodenum, obviously a rare condition inasmuch as only 5 other cases are mentioned in the literature. In most of the reported cases the tumor occurred in the third portion of the duodenum. It is of interest that in these cases roentgenograms offered no diagnostic aid, with a single exception. In every case the tumor was very large but did not cause stenosis or dilatation of the bowel. Surgical removal was extremely dangerous because of probable damage to the superior mesenteric artery or its branches with subsequent changes in the bowel. Four of the patients were operated on, and 5 of the 6 patients died of pulmonary embolism or pulmonary thrombosis.

Two cases of diverticulum of the duodenojejunal junction are recorded by Raven⁷⁴ and are of interest only because of the rarity of a diverticulum occurring in this position.

Weiss⁷⁵ discusses the etiologic factors of megaduodenum and reports on the abnormality as observed in 6 members of the same family during three generations. In 5 of these 6 patients there were associated congenital abnormalities. In discussing the condition he notes that persons in whom it is congenital may remain symptom free for years, and he advises only conservative treatment for those patients who complain

72 Lieber, M. M., Stewart, H. L., and Lund, H. Carcinoma of Prepapillary Portion of the Duodenum, *Ann Surg* **109** 383, 1939.

73 Foshee, J. C., and McBride, W. P. L. Leiomyosarcoma of the Duodenum. Report of a Case and Review of the Literature, *J A M A* **112** 2497 (June 17) 1939.

74 Raven, R. W. Diverticula of the Duodenojejunal Flexure, *Lancet* **1** 203, 1939.

75 Weiss, W. Zur Aetiologie des Megaduodenum, *Deutsche Ztschr f Chr* **251** 317, 1938.

of mild peristaltic disturbances. He expresses the opinion that surgical intervention may be necessary if the symptoms are serious but quite correctly states that gastroenterostomy, duodenojejunostomy and a Billroth II type of operation with a terminolateral gastroenterostomy all fail to help. He advocates modification of the Billroth II operation as devised by Roux. It is important to point out, however, that the most favorable results reported in relation to surgical treatment in this condition are probably examples of wishful thinking, and surgical measures should be considered only after all other methods have failed to provide reasonable control.

Increased interest in diseases of the small bowel has been obvious during recent years. With improved methods of roentgenologic examination, possibly with intubation of the small bowel and with closer attention to the exact reference of the pain experienced in these conditions, there is no doubt that more accurate diagnoses are possible than previously. Lesions such as those reported by Shaw can frequently be localized, even though their exact nature cannot be definitely diagnosed. Reference is made to his article merely because of the importance of considering the somewhat unusual but not too infrequent lesions of the small bowel. Shaw⁷⁶ reports 5 cases of polyposis of the small intestine, a relatively rare clinical entity but of importance because of the tendency toward malignant degeneration. Preoperative diagnosis is difficult, largely because early signs and symptoms are insufficient to cause patients to consult a physician. Frequently such lesions are first brought to the attention of the surgeon because of an abdominal crisis caused by intestinal obstruction from intussusception. It is worthy of remark that patients suffering from these and similar lesions frequently complain to a doctor of umbilical distress, which in itself is a symptom that should always call attention to the possibility of disease of the small intestine.

Ileitis continues to be the subject of numerous articles, but little has been added to knowledge of the disease except as to its clinical manifestations. An unusual report is that of Brown and Scheiffly,⁷⁷ who present data on 3 siblings, 2 sisters and a brother, who exhibited various manifestations characteristic of regional enteritis. A second brother was known to have intestinal disturbances presenting many similar features, but permission to examine his colon and ileum have not been obtained. The report is of interest inasmuch as it is extremely rare for either colitis or enteritis to occur in more than one member of a family. In commenting on the treatment of the disease the authors

76 Shaw, E. A. Polyposis of the Small Intestine. Report of Five Cases, *New England J. Med.* **220** 236, 1939.

77 Brown, P. W., and Scheiffly, C. H. Chronic Regional Enteritis Occurring in Three Siblings, *Am. J. Digest. Dis.* **6** 257, 1939.

consider that resection of the diseased portion of the bowel is the therapeutic procedure of choice at present but express the hope that a better understanding of this unusual condition may in the future offer a less radical treatment

This conservative point of view as regards therapy of regional enteritis is one that is occasionally voiced, and reports similar to that of Kross⁷⁸ must not be overlooked. He reports the results in 3 cases in which the bowel was operated on to an extent which would usually be considered inadequate. In the first patient only the appendix was removed and the diseased bowel was left undisturbed, a second patient had only an enterostomy, and the third, a "side-tracking" colostomy. These patients had no recurrences during periods of five and a half, four and three-quarters and one and a quarter years, respectively. Although numerous instances can be obtained of fairly or very satisfactory responses to conservative medical management of the condition, it is obvious that in the present state of knowledge surgical operation must constitute an important form of therapy.

Because of suggestive clinical and experimental evidence that the disease may originate in the mesenteric lymphatics, Mixer and Starr⁷⁹ believe that the successful results following resection of the affected ileum depend primarily on wide excision of the involved mesentery and its lymph nodes. They also believe that failure to carry out this type of treatment may bear a definite relation to the recurrences frequently observed after surgical treatment.

The question of the amount of small bowel that can be safely resected is particularly pertinent to the subject of ileitis. Various studies have appeared from time to time on food absorption in patients who have had portions of the bowel removed. West and co-workers⁸⁰ present such studies on digestion and absorption in a man with 3 feet (90 cm) of small intestine. This patient had five resections of the small bowel over a period of eleven years, with less than a foot (30 cm) of jejunum remaining. At exploration, several months prior to metabolic studies, the remaining small bowel was found to be dilated and hypertrophied almost to the size of the normal large intestine. It was found that under the existing conditions about 25 per cent of the ingested protein and 45 per cent of the fat were lost in the feces, representing approximately 25 per cent of the caloric value of ingested food. Practically all of the carbohydrate in the diet was absorbed.

78 Kross, I. Terminal Ileitis. Conservative Surgical Treatment, *Am J Digest Dis* **5** 313, 1938.

79 Mixer, C. G., and Starr, A. Further Experience with Regional Enteritis, *New England J Med* **219** 37, 1938.

80 West, E. S., Montague, J. R., and Judy, F. R. Digestion and Absorption in Man with Three Feet of Small Intestine, *Am J Digest Dis* **5** 690, 1938.

and utilized. A high calcium and viosterol intake was necessary in order to keep the man in a positive calcium balance, and, with what was apparently only about one sixth of the small bowel remaining a fairly satisfactory existence was possible. Fat absorption would appear to be the chief limiting factor necessitating anything like the normal length of small bowel. The regulation of diet in this case may well be utilized as a guide to the dietary treatment of patients with similar conditions.

The causes of ileus of the small intestine are well known. Two recent reports are of some interest in this connection. Adamson and Hild⁸¹ report the development of complete obstruction of the ileum in an infant within thirty-six hours after birth. The obstruction was primarily due to a packing of the lower 18 inches (45.5 cm) of the ileum with inspissated waxy meconium and associated intussusception below the mass. Twenty-two other cases are reported in the literature although the condition must be considered as a rarity.

Another unusual report is that of Badertscher,⁸² who describes a triple intussusception of the ileum in a child as a result of an automobile injury. This case report is only the fourth in the literature of traumatic intussusception, although numerous cases of multiple intussusception in children have been described. Laparotomy showed the ileum to be intussuscepted in three places. Reduction was possible, with complete recovery.

The diagnosis of partial or complete intestinal obstruction is still a problem to be solved largely on the basis of clinical experience. It is true, however, that many physicians are still unaware of the diagnostic help that can be obtained from the roentgenologist once the condition is suspected. Although there is little, if anything, new in the article on roentgen diagnosis of complete and partial intestinal obstruction by Solis-Cohen and Levine,⁸³ the importance of this diagnostic procedure is properly emphasized. They stress the extreme diagnostic importance of flat or survey roentgenograms of the abdomen in the early stages of acute intestinal obstruction and the need for examining patients in the prone, supine and upright positions. With other roentgenologists they agree that the absence of a stepladder appearance does not rule out ileus and indicate that they consider the appearance of trapped gas and haupin turns as among the earliest signs of acute intestinal obstruction. Excellent illustrations accompany the article.

81 Adamson, E. W., and Hild, J. R. Meconium Ileus, *J. A. M. A.* **112** 2275 (June 3) 1939.

82 Badertscher, V. A. Traumatic Triple Intussusception of the Ileum in a Child, *J. A. M. A.* **112** 422 (Feb. 4) 1939.

83 Solis-Cohen, L., and Levine, S. X-Ray Diagnosis of Complete and Partial Acute Intestinal Obstruction, *Radiology* **31** 8 1939.

Another detailed discussion of roentgen signs to be observed in this condition is presented by Høyer,⁸⁴ who gives a particularly full description of the roentgen signs to be noted in the first twenty-four hours of obstruction of the small bowel, before the development of diagnostic clinical signs and symptoms. He reviews the details of Kloiber's original studies of 100 cases and illustrates the findings to be made by roentgenologic examination without contrast mediums in his own 46 cases. He stresses the importance of fluoroscopic examination for noting changes in the fluid levels as an important differential point between mechanical and paralytic ileus. Among other important diagnostic points he mentions the more or less complete absence of gas from the large bowel in the presence of an obstruction of the small bowel.

The treatment of intestinal obstruction by intubation is again considered by Abbott.⁸⁵ The technic for intubation of an obstructed bowel, he has previously described. Observations on 27 patients are presented, and the entire article, including a discussion of the condition, is extremely sound and clinically important. The data, together with the enclosed diagrams and roentgenograms, are convincing. The author points out that passage of a tube to the point of obstruction is of particular value because it converts a situation calling for emergency measures into one in which the time of operation, if this is performed at all, becomes a matter of election. He recognizes that the great contraindication to intubation is gangrene and that success with the procedure therefore demands excellent clinical judgment. Failure to relieve symptoms as the intubation proceeds should be the indication for a decision to operate. If, on the other hand, pain and vomiting abate following intubation, and there is disappearance of distention, time is gained for further study and for insuring proper nourishment of the patient. Abbott concludes from his observations:

Intubation not only rarely adds to the hazards of acute intestinal obstruction, but frequently improves the condition of the patient, increases his comfort, enables the physician to determine the character of the obstructing lesion, simplifies its resection when that proves necessary, safeguards convalescence, and above all contributes to safety by converting an emergency condition into one completely under the physician's control.

The prevention of paralytic ileus following operation is discussed in an interesting article by Cairney,⁸⁶ who does not include ileus due to

84 Høyer, A. X-Ray Diagnosis of Intestinal Obstruction, *Acta radiol* **19** 409, 1938.

85 Abbott, W. O. Intubation of the Human Small Intestine. The Treatment of Intestinal Obstruction and a Procedure for Identifying the Lesion, *Arch Int Med* **63** 453 (March) 1939.

86 Cairney, J. Prevention of Paralytic Ileus, *New Zealand M J* **37** 334, 1938.

peritonitis Although the article describes no new measures, the author summarizes therapeutic procedures in a logical manner and one worthy of presentation Morphine is administered if needed during the first forty-eight hours after operation On the third morning Canney examines the abdomen with a stethoscope for evidences of peristalsis If this is present, an enema is given, and if good results are obtained, the enema is followed by an aperient If peristalsis is absent and distention is commencing, prostigmine and acetylcholine are administered, followed by an enema Morphine is given only at night, for crampy pain If no peristalsis and no distention are present, one has the choice of employing an enema or first using prostigmine and acetylcholine Canney warns against using an aperient until satisfactory results have been obtained by an enema

Demidova⁸⁷ in one of several articles published in a symposium on acute ileus describes changes in the blood picture in this condition and in incarcerated hernia In 100 cases of incarcerated hernia there was a moderate increase in the number of red cells and the percentage of hemoglobin before the possible appearance of dehydration The author thinks that these changes were due to stimulation of the vegetative nervous system with an outflow of red blood cells from reserve depots These changes are accompanied by mild leukocytosis In 158 cases of acute intestinal obstruction an elevation of the red blood cell count was noted up to 6,000,000, of the hemoglobin up to 120 per cent and of the white blood cell count up to from 12,000 to 30,000, with a distinct shift of neutrophils to the left In the cases of ileus of the small bowel the increases in the number of red cells, hemoglobin and white cells were never more marked than the corresponding increases observed in an equal number of cases of obstruction of the sigmoid The author concludes that the blood picture reflects three stages of obstruction (1) a slight initial increase of red cells, hemoglobin and white cells, due to initial pain and irritation with stimulation of the vegetative nervous system, (2) a subsequent rise, which he attributes to intoxication, dehydration and an increase in the viscosity of the blood, (3) with beginning infection, peritonitis and further intoxication and subsequent leukopenia

Another well worn subject that of late has deservedly attracted a great deal of attention is appendicitis In spite of innumerable articles on the subject, mortality from this cause remains at an appallingly high figure, and it is to be noted with regret that, if anything, there is a higher mortality from appendicitis among physicians than among the laity Among numerous articles, a few have been chosen Kelly

⁸⁷ Demidova, P. N. Blood Picture in Acute Ileus. *Vestnik khir* 56 356, 1939

and Watkins⁸⁸ present an interesting review of the results in 1,000 consecutive cases of acute, simple and chronic appendicitis in which operations were performed within recent years and contrast the results with those obtained in 1,000 similar cases reported by the same authors in 1931. The results in the series under discussion show no great variation from those previously reported except for a sharp increase in the death rate noted for those classified as instances of the acute suppurative type of appendicitis. This increase rose from 9 per cent in the first series of cases to a mortality of 23 per cent in the group under discussion. The authors believe that this rather alarming increase in mortality is due to a delay in operating because of economic changes during the depression years and a tendency to use home remedies, including purgatives, as well as to factors complicating diagnosis. The same increase in the number of deaths from acute appendicitis is noted in an entirely similar report made by Quain and Waldschmidt on two 1,000 case studies reported in 1928 and 1934, respectively. These authors reported a mortality of 18.8 per cent during the depression years, as compared with a mortality of 10 per cent prior to that time.

The question of deferring operation in the presence of peritonitis due to rupture of an acutely inflamed appendix in a child is discussed by Elman⁸⁹. The decision to postpone operation, he thinks, depends not so much on the presence or absence or degree of peritonitis as on the general condition of the child. In a group of 181 children operated on for peritonitis following rupture of an acutely diseased appendix the total mortality was 15.5 per cent. Thirty-three were classified as extremely toxic, and, of the remaining patients, only 9 succumbed, making a mortality of 6 per cent in the nontoxic group. The mortality was 70 per cent in those operated on at once and only 30 per cent in those operated on after a delay of from nine to twenty-four hours, whereas in the nontoxic group the condition was reversed, a delay in operation causing a 15 per cent mortality as opposed to a mortality of only 3.5 per cent in those children operated on immediately. These figures seem extremely high in the face of another report by Bruce,⁹⁰ who operated on 467 children suffering from acute appendicitis, with a total mortality of only 1.9 per cent, until one realizes that Elman's patients were selected from a group whose appendixes had ruptured.

88 Kelly, F. R., and Watkins, R. M. Appendicitis in Adults. Review of Two Thousand Consecutive Cases, with Comments on the Rising Mortality of the Acute Suppurative Type, *J. A. M. A.* **112** 1785 (May 6) 1939.

89 Elman, R. Peritonitis Due to Ruptured Acute Appendicitis in Children. Influence of Delay in the Operative Mortality, *Am. J. Digest. Dis.* **5** 804, 1939.

90 Bruce, G. G. Diagnosis and Treatment of Acute Appendicitis in Children, *Lancet* **1** 1247, 1939.

Love⁹¹ considers that in those cases of appendicitis in which there is a palpable mass this is due either to abscess or to local peritonitis. In discussing the danger of immediate operation he reports an average mortality of 6 per cent or more, as opposed to an average mortality of under 3 per cent in cases in which he used expectant medical treatment. He is careful to point out that expectant treatment is not particularly suitable for children and old people.

The numerical importance of appendicitis among college students has received much attention in recent years, and an illuminating article is that of Schmidt and Joachim,⁹² who reported on 1,303 students with appendicitis encountered at the University of Wisconsin.

The question of the treatment of the chronically disturbed appendix continues to receive consideration, but little, if anything new or important has been presented. An undoubtedly correct point of view is that of Swalm and Morrison,⁹³ who plead for a conservative attitude toward appendectomy for "chronic appendicitis." They stress particularly the infrequency with which this condition is correctly diagnosed in the presence of the syndrome of a spastic, irritable or unstable colon.

Reference should also be made to a thoughtful study by Shelley⁹⁴ of 881 cases of "chronic appendicitis." Shelley believes that he has adequate evidence that such a clinical entity exists, but he emphasizes the extreme importance that should be paid to a definite localization of physical findings and to the nature and frequency of attacks. Although presenting an obviously surgical point of view, the author is extremely careful to insist on the utmost diagnostic care in ruling out other conditions simulating appendicitis. The article is well worthy of careful perusal.

Intestinal tuberculosis still presents difficulties in diagnosis and treatment. Tsigelnik⁹⁵ discusses in some detail 150 cases of this condition and points out one important factor, namely, that symptoms were entirely absent in 6 of 50 persons who came to autopsy with this diagnosis and for whom the diagnosis was confirmed. Of the 150 cases, roentgen study following a barium sulfate meal and enema gave positive results in 80 per cent, occult blood was noted in the stools in 18 per cent, and hypochromic anemia (hemoglobin under 60 per cent) was

91 Love, R. J. M. The Appendix Mass, *Lancet* **1** 1252, 1939.

92 Schmidt, E. R., and Joachim, F. G. The Student Health Problem of Appendicitis. Report of 1,303 Cases at Student Infirmary and Wisconsin General Hospital, *Journal-Lancet* **58** 329, 1938.

93 Swalm, W. A., and Morrison, L. M. Plea for Conservatism in Appendectomy for Chronic Appendicitis. Observations on the Spastic, Irritable or Unstable Colon Syndrome, *Pennsylvania M. J.* **41** 988, 1938.

94 Shelley, H. J. Chronic Appendicitis. Is It a Clinical Entity? *Arch Surg* **37** 17 (July) 1938.

95 Tsigelnik, A. Y. Intestinal Tuberculosis, *Sovet vrach zhur* **43** 977, 1939.

noted in 80 per cent. Of 50 cases in which treatment was by pneumoperitoneum, the author reports that remission for a period of twelve months or more was obtained in 32. Like other writers, he stresses the importance of an attempt at prophylaxis of intestinal tuberculosis through correction of habitual constipation, instructions not to swallow any sputum and collapse therapy to render the sputum bacillus free.

In a rather poorly written article on the same subject Hardt and his collaborators⁹⁶ report some observations of interest on the treatment of intestinal tuberculosis in 238 cases. Favorable results are attributed by the authors in part to the administration of calcium gluconate by mouth, intravenously or intramuscularly. Ultraviolet radiation is thought to have aided the favorable results obtained by the use of calcium. As in the preceding article, collapse therapy is mentioned as an important factor in the treatment of gastrointestinal tuberculosis, probably through improvement in the pulmonary condition and a resulting decrease in the number of bacilli in the sputum. These authors also emphasize the necessity of consistent and careful expectoration as a prophylactic measure. It seems possible that the advantages of calcium therapy are somewhat overemphasized by these workers inasmuch as of 163 patients showing improvement in gastrointestinal symptoms, 134 had received collapse therapy.

A review of the therapeutic aspects of the treatment of intestinal tuberculosis is presented by Mayer and Dworkin,⁹⁷ who point out the excellent results frequently obtained by the cautious use of roentgen and the enthusiastic use of ultraviolet therapy.

Charr and Cohen⁹⁸ have determined the incidence of intestinal tuberculosis in necropsy studies of patients who died of tuberculous anthraco-silicosis and patients who died of pulmonary tuberculosis without anthracotic involvement. The incidence of intestinal tuberculosis was approximately 50 per cent in the subjects without anthracosis, whereas it occurred in only 20 per cent of patients showing anthracosis as well as pulmonary tuberculosis.

An interesting clinical report on disease of the small bowel is found in an article by Wolpaw,⁹⁹ in which he describes 3 cases of ulcerative hyperplastic tuberculosis of the small intestine. Although this is occasionally a cause of intestinal obstruction, its rarity, together with the fact

96 Hardt, L. L., Weissman, M., Coulter, J. S., and Henrichsen, K. J. Treatment of Gastrointestinal Tuberculosis, *J. A. M. A.* **112** 691 (Feb 25) 1939.

97 Mayer, E., and Dworkin, M. Roentgen and Light Therapy of Intestinal and Peritoneal Tuberculosis, *Radiology* **31** 35, 1938.

98 Charr, R., and Cohen, A. C. Tuberculosis of Intestines in Tubercular Anthraco-silicosis, *Am. J. M. Sc.* **196** 83, 1938.

99 Wolpaw, S. E. Isolated Hyperplastic Ulcerative Tuberculosis of the Small Intestine, *Am. Rev. Tuberc.* **38** 32, 1938.

that as a rule it is unaccompanied by evidence of active pulmonary disease, makes the report of importance. This is particularly so because a reasonably early diagnosis of the condition may frequently be followed by successful surgical removal of the local lesion.

LARGE INTESTINE

The physiology of the large intestine has been studied by Jackman and Baigen,¹⁰⁰ who introduced a balloon into the human colon through a colostomy opening and observed the effect of various drugs commonly used to lessen the tone of the musculature of the bowel. Of the spasmolytic drugs employed, glyceryl trinitrate and amyl nitrite were found to be the most consistently efficacious in decreasing the motility of the large bowel. The increase in tone following the use of morphine, as noted by other investigators, was again demonstrated, and it appeared that benzedrine sulfate did not result in any great decrease in bowel tone. Syntropan (a phosphate of 3-diethylamino-2,2-dimethylpropylester of tropic acid) and trasantin (a synthetic ester of diphenylacetic acid and diethylaminoethanol), synthetic chemical substances resembling atropine, appeared to be as effective antispasmodics as atropine, without the undesirable toxic effects of the latter. It is to be noted, however, that benzedrine, syntropan and trasantin were administered intramuscularly, a method of administration that is not ordinarily employed therapeutically. There is still a real question as to the therapeutic efficiency of these newer synthetic preparations when administered by mouth. The fact that they are more expensive and possibly no better than simple atropine derivatives should be remembered in recommending their use.

The same authors¹⁰¹ carried out further studies on the influence of papaverine on the muscular tone of the intestinal tract. Papaverine hydrochloride alone or combined with pantopon (a mixture of the hydrochlorides of the opium alkaloids) has seemed to be of value in relieving the abdominal cramps and frequent purulent bloody discharges in colitis. The evidence obtained experimentally by Baigen and Jackman substantiated the antispasmodic effect of the papaverine compound. It appears that it has certain advantages over morphine sulfate in cases in which one desires to immobilize the intestine or put it at rest.

The findings of Beyer and Meek¹⁷ in a study on the effect of benzedrine sulfate on intestinal activity are in agreement with those of other investigators. Only by using excised intestinal strips and high concentrations of the drug could they demonstrate any effect on the intestine.

100 Jackman, R. J., and Baigen, J. A. Influence of Certain Antispasmodic Drugs on Intestine of Man, *Surg., Gynec. & Obst.* **67** 63, 1938.

101 Baigen, J. A., and Jackman, R. J. Influence of Papaverine on Muscular Tone of the Intestinal Tract, *Surg., Gynec. and Obst.* **68** 749, 1939.

Further studies on the effect of certain parenterally administered drugs on the colon of the dog were carried out by Wolff¹⁰² A series of experiments were performed on trained unanesthetized dogs having Thiry or Wella colonic fistulas, in order to determine the effect of a number of drugs on the motility of the colon The drugs were administered parenterally, and recordings were obtained by means of rubber balloons with a kymographic recording apparatus It was found that calcium salts, physostigmine, hypertonic salt solution and acetylcholine produce increased tone and increased motility Solution of posterior pituitary U S P, pitocin, pitressin, ephedrine, histamine and epinephrine cause decreased tone and decreased motility Pitocin produces the most striking depressive effect Hypertonic solution of dextrose and parathyroid extract have little or no effect on colonic motility Physostigmine and ephedrine used together produce marked stimulation of colonic motility as do also physostigmine and acetylcholine administered simultaneously

The effect of karaya gum on colonic activity was studied clinically by Ivy and Isaacs¹⁰³ in a group of 23 patients The authors studied the action of the gum, a hygroscopic substance which absorbs water and expands considerably, and noted that it absorbs and holds a large quantity of water and causes only a negligible amount of fermentation It is not appreciably disintegrated in the alimentary tract and does not appreciably affect digestion of starch or inhibit utilization of vitamin A It does tend to increase fecal excretion of nitrogen to some extent, and in animals as well as in human beings it causes an increased number of defecations, increases the bulk and moisture of the stools and does not cause any detectable irritation It relieved constipation in about 80 per cent of the persons in whose treatment it was used Ivy and Isaacs conclude that it produces no harmful effects and is not habit-forming and that it may prove a valuable addition to the treatment of patients with intestinal difficulties

An unusual study on the physiology of the alimentary tract is that reported by Maddock and Heath¹⁰⁴ on the excretion of iron from the digestive tract A histologic study of the entire digestive tract of the dog and of an explant of the colon before and after administration of iron revealed no evidence that iron can be observed in the process

102 Wolff, L H The Effect of Certain Parenterally Administered Drugs on the Colon of the Dog, *Am J Digest Dis* **6** 243, 1939

103 Ivy, A C, and Isaacs, B L Karaya Gum as a Mechanical Laxative An Experimental Study on Animals and Man, *Am J Digest Dis* **5** 315, 1938

104 Maddock, S, and Heath, C W Is Iron Excreted by the Gastrointestinal Tract of the Dog? A Histologic Study, *Arch Int Med* **63** 584 (March) 1939

of excretion. Traces of iron seen in the walls of the stomach and large bowel were considered to be in a state of storage rather than of excretion.

Ulcerative colitis, as usual, has received a large amount of attention and it is becoming apparent that the nature and history of the disease is more clearly understood at the present time than in recent years. It seems fair to state that the causes of the condition are still unknown, although various workers have attempted to find a causative organism. There is almost complete agreement that the diplostreptococcus group of Baigen is probably a secondary invader, and attempts to prove that *Bacillus dysenteriae* is the usual responsible agent are still far from convincing. An excellent symposium on the entire subject has been presented by Mackie,¹⁰⁵ Jones¹⁰⁶ and Willard and associates.¹⁰⁷ In these three articles the question of therapy is fairly completely covered from both medical and surgical points of view. A perusal of the discussion in this symposium should be of real value to those interested in this disease, a malady which presents one of the most difficult problems of the day. The conclusions in Mackie's paper may well be quoted:

1 Chronic ulcerative colitis appears to be the complex expression of the interaction of several different factors

2 The disease exhibits an inherent tendency to progression and relapse

3 Although the prognosis under medical management is good in the pathologically mild and moderately advanced case, the term "apparently arrested" should be substituted for "cured"

4 Prolonged joint medical and surgical observation is essential for the pathologically advanced case

5 Combined medical and radical surgical treatment offers the best prognosis for many of the pathologically advanced cases

Jones comments on the extremely bad prognosis of the so-called fulminating form of the disease, a type that usually can be recognized by the curious velvety, diffusely oozing appearance of the rectum and rectosigmoid at sigmoidoscopic examination. Such a condition, as a rule, responds badly to either medical or surgical measures. Among other important points noted in the discussion by Willard and collaborators is the fact that the extent of involvement as shown in roentgenograms does not constitute a reliable prognostic sign. Mackie and the other writers point out the absolute necessity for a close correlation

105 Mackie, T. T. Medical Management of Chronic Ulcerative Colitis, *J. A. M. A.* **111** 2071 (Dec. 3) 1938

106 Jones, T. E. Surgical Treatment of Ulcerative Colitis, *J. A. M. A.* **111** 2076 (Dec. 3) 1938

107 Willard, J. H., Pessel, J. F., Hundley, J. W., and Bockus, H. L. Prognosis of Ulcerative Colitis, *J. A. M. A.* **111** 2078 (Dec. 3) 1938

between medical and surgical management in dealing with these patients, who present all the extreme manifestations of deficiency disease and chronic infection

Among various articles contributing to a better understanding of the disease, attention should be directed to that of Paulson,¹⁰⁸ who discusses the confusion frequently existing in the consideration of rectal lesions due to lymphogranuloma venereum and idiopathic ulcerative colitis or other rectal lesions associated with stricture. Paulson discusses experimental and clinical evidence which supports the view that the virus of lymphogranuloma venereum found in intestinal discharge (bowel antigen) or tissue (bowel tissue antigen) is of pathogenic significance. When the bowel antigen reaction is positive it indicates that the virus of lymphogranuloma venereum is in the bowel tissue or the discharge from which it is obtained. He claims that the only direct clinical method now available to determine the presence of the virus in such sources is in the use of bowel antigen. Bowel antigen is important, because the clinical picture is not pathognomonic, and the so-called lymphogranuloma venereum is not always caused by the virus of this disease. In some cases a condition clinically indistinguishable from nonspecific ulcerative proctitis and colitis is found in association with the virus of lymphogranuloma venereum by means of bowel antigen. The pathologic picture grossly and histologically is not pathognomonic, and the use of bowel antigen may aid in the differential diagnosis. The use of Frei antigen alone in difficult cases is not adequate, because the patient may give no reaction to the Frei antigen, whereas bowel antigen may indicate the presence of the virus (aneigy). A positive Frei reaction may be produced by an antedated or healed virus infection or by one completely unrelated to the existing bowel disturbance. Paulson's observations are of more than speculative interest and may help to differentiate another small but important group of cases of so-called idiopathic ulcerative colitis.

One of the most important contributions to an understanding of the subject is found in the brilliant observations of Lium.¹⁰⁹ Using a method of colonic explantation, Lium was able to demonstrate in dogs, by direct visualization of the colonic mucosa, that the explants reacted to various stimuli by spasm of the colonic musculature. Whether produced by mechanical stimulation, parasympatheticomimetic drugs or dysentery toxin, this spasm resulted in damage to the overlying epithe-

108 Paulson, M. Bowel Antigen. Clinical Use of a New Method to Determine the Presence of Virus of Lymphogranuloma Venereum in the Differential Diagnosis of Intestinal Involvements, *J A M A* **112** 1788 (May 6) 1939

109 Lium, R. Etiology of Ulcerative Colitis. Effect of Induced Muscular Spasm on Colonic Explants in Dogs, with Comment on Relation of Muscular Spasm to Ulcerative Colitis, *Arch Int Med* **63** 210 (Feb) 1939

lial structure, with resultant hemorrhage and ulceration. The mode of action of dysentery toxin in producing ulcerations of the mucosa is thus apparently through the injurious effects of smooth muscle spasm. In association with muscular contractions of the explant the secretion of mucus is immediately increased. When muscular hyperactivity continues, only thin, watery material, inadequate for protective purposes is secreted. Ulcerated areas are not covered with a coating of mucus until they have healed, thus being exposed to trauma from the passing current. Even after returning to a normal gross appearance, the regenerating epithelium is more sensitive to trauma than the normal epithelium of a colonic graft. Lium discusses the possibility that ulcerative colitis may be conceived as a specific reaction to a number of influences which can initiate spasm of the colonic musculature. These include possible hyperactivity of the parasympathetic nervous system, infections such as bacillary dysentery and vitamin deficiency. Once the colon becomes spastic, it is an organ that can produce damage to its own surface structures. Exhaustion of the secretion of mucus, together with nutritional deficiency, may contribute to the prevention of healing. That muscular spasm may be responsible for lesions of the mucosa of other portions of the gastrointestinal tract is suggested by certain of the experiments under discussion, as well as by a reinterpretation of the work of others.

Lium and Porter¹¹⁰ contribute an important analysis of 6 fatal cases of ulcerative colitis. Stool cultures and agglutinations for dysentery were negative in 5 of the 6 cases. Of the observations at necropsy that were considered to be of importance, the chief was the distribution of the lesions. At the junction of the rectum and sigmoid the ulcerations developed in three rows running longitudinally. In places the ulcerations extended between the longitudinal rows of ulcers and seemed to follow a linear pattern, which was found to lie directly over the tenial bands. In addition to the usual histologic features, special attention was directed to the absence or marked diminution of mucus in the epithelial cells in early lesions, observed in all sections. The arrangement of the most severe lesions in ulcerative colitis is such that they lie directly over the most powerful muscles in the colon and the authors suggest that there may be a distinct relationship between the muscles and the lesions. The early stage of ulcerative colitis can be simulated experimentally in animals by hypermotility and spasm of the colonic muscles, features that are prominent in the disease. The authors conclude: "It seems highly probable that ulcerative colitis is primarily

110 Lium, R., and Porter, J. E. Observations on the Etiology of Ulcerative Colitis. III. Distribution of Lesions and Its Possible Significance, *Am J Path* 15: 73, 1939.

a disease caused by intense muscular spasm and hypermotility, and that therefore the distribution of the lesions follows a muscular pattern. Whatever infectious element is present may well be due to secondary involvement of damaged areas caused by muscular overactivity." It is not difficult to draw an inference from a comparison between these striking observations of Lium and Porter and the many cases in which ulcerative colitis appears to have its origin in an unstable and overstimulated autonomic nervous system. The changes visualized by Lium following the action of parasympathetic drugs are not dissimilar to those reported by White and Jones and bear a direct relationship to the clinical observations of Sullivan, Murray and others.

Further clinical confirmation of the importance of considering individual reactions in relation to ulcerative colitis is contributed by Wittkower,¹¹¹ who presents a psychologic analysis of 40 patients with ulcerative colitis. In 37 of these, psychologic abnormalities and disorders were present that were far beyond the range of individual differences observed in the average population and were found to antedate the initial symptoms of the colitis. Of these 37 patients, 17 had obsessions, 12 had gross hysteria, and 6 were classified as persons of schizoid or depressive mentality. There were no universally common precipitating conflicts, but the authors suggest that the psychologic factor seems to be the most constant cause in this disease, although admitting that the etiologic problem is far from being solved. They conclude that observation of patients with ulcerative colitis appears to justify an attempt at psychotherapy for selected ones with early forms of this disease, a conclusion that is in accordance with the opinion of others. It should be pointed out, however, that psychotherapy should be instituted with extreme caution inasmuch as there is real danger that during the course of treatment the symptoms of colitis may be aggravated to a dangerous degree.

Specific measures for the medical treatment of this disease continue to accumulate in much the same way that ulcer therapy has progressed in recent years. Cheney,¹¹² following the suggestion that deficiency plays an important role in ulcerative colitis, reports on 8 patients treated by large injections of concentrated liver extract and thiamin chloride. In the majority of these other methods of treatment had failed to be of benefit, and in all satisfactory remissions were obtained, with clinical and sigmoidoscopic improvement. Although there can be little doubt that satisfactory remissions accompanied the administration of liver

111 Wittkower, E. Ulcerative Colitis. *Personality Studies*, Brit. M. J. **2** 1356, 1938.

112 Cheney, G. Injections of Highly Concentrated Liver Extract in Treatment of Idiopathic Ulcerative Colitis, *Arch. Int. Med.* **63** 813 (May) 1939.

extract, to which the author gives credit, it is important to remember that similar remissions occur spontaneously and frequently in this disease. It should be pointed out that, although credit is given to liver extract, in reality the treatment included the administration of large amounts of vitamin B₁ in addition to the use of the medical measures that are commonly employed. Cheney's conclusions are at best speculative, and while no means of procuring improvement in this dangerous disease should be overlooked, one feels that the interpretation of his results should be more guarded.

Another report of therapeutic interest is that of Gainsborough¹¹³ who treated 6 patients by cod liver oil retention enemas. The author frankly states that the method was not certainly curative, but he believes that it was efficacious in shortening the illness in some patients and in reducing pain. He points out that these patients were more tolerant to cod liver oil enemas than to other local applications, a statement that causes one to question whether as a therapeutic measure the method is not merely palliative, although as such it should be regarded as a possible valuable adjunct to therapy.

The degree of deficiency that may occur during the course of ulcerative colitis is reemphasized by Lerner and Rapaport¹¹⁴ who describe the results of biophotometric studies in 30 persons suffering from this disease. Approximately one third of the patients showed evidence of inability to adapt normally in the dark, a larger percentage than is found in any general hospital group. The conclusion seems justified that avitaminosis A constitutes one of the complications encountered in this disease and emphasizes the necessity for intensive vitamin therapy.

Although the use of pectin has, for several years, been advocated as an important therapeutic measure in the treatment of ulcerative colitis, the experience of most clinicians has not been particularly favorable. Recent articles, however, by Block and associates¹¹⁵ and by Arnold¹¹⁶ suggest the possible therapeutic value of nickel pectinate as a therapeutic measure worthy of trial. Block and associates present a comparative study of the effects of pure pectin and nickel pectinate administered to 95 patients with bacillary dysentery. Pure pectin was found to be ineffective, but definite improvement was observed in every

113 Gainsborough, H. Treatment of Ulcerative Colitis by Cod Liver Oil Retention Enemata, *Lancet* **1** 1319, 1939.

114 Lerner, H. H., and Rapaport, H. G. Biophotometric Studies in Thirty Cases of Chronic Ulcerative Colitis, *Am J Digest Dis* **6** 239, 1939.

115 Block, L. H., Tarnowski, A., and Green, B. H. Pectin and Nickel Pectinate in Acute and Chronic Bacillary Dysentery, *Am J Digest Dis* **6** 96, 1939.

116 Arnold, L. Influence of the Ingestion of Nickel Pectinate upon Growth of Young Rats, *Am J Digest Dis* **6** 103, 1939.

patient following the use of nickel pectinate. Improvement was apparent in the appearance and general condition of the patients and was accompanied by the disappearance of acute symptoms, tenesmus and bloody diarrhea and by an increase in weight. There seemed to be no contraindications to its use, and no allergic or untoward reactions were observed following the administration of the drug. Arnold, in animal experiments, confirmed the finding of lack of toxicity in nickel pectinate administered in large doses to young rats. There was no interruption of the growth over an eight week period of observation, and no pathologic changes were demonstrable. He further apparently shows by *in vitro* experiments¹¹⁷ that many of the metal pectinates possess definite bactericidal activity, although pure pectin seems to show none. Of the preparations studied, silver pectinate possesses the greatest bactericidal activity of any, but nickel pectinate also shows some. It is of some interest that different metal pectinates apparently have individual bactericidal powers that vary with different organisms, such as *Bacillus typhosus* and *Bacillus coli*.

It was to be expected that sulfanilamide and sulfanilamide derivatives would be tried in the treatment of such a chronic and dangerous disease as ulcerative colitis. Although it is altogether too early to draw conclusions on the efficacy of such therapy, at least from published data, the article by Bannick and associates¹¹⁸ is of interest. In a preliminary report they suggest the use of neoprontosil (disodium 4-sulfonamido-phenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3', 6' disulfonate) and suggest that the prompt subsidence following the use of the drug in milder conditions was due to this particular medication. They recognize, however, the characteristic occurrence of spontaneous remissions and are extremely cautious in drawing any conclusions. They have no hesitation in suggesting that the drug may be useful in milder forms of the disease and that it may help to bring about improvement in the underlying condition. Further studies with this particular therapeutic agent will be of extreme interest.

While discussing diseases of the large bowel it is proper to refer to a report by Mansans¹¹⁹. This concerns only a single pedunculated rectal tumor, but the conclusions drawn from the case are of direct clinical importance. The rectal tumor was removed by diathermy, and the procedure was followed by the development of peritonitis and death.

117 Arnold, L. The Bactericidal Action of Pectin and Metal Pectinates, *Am J Digest Dis* **6** 104, 1939

118 Bannick, E. G., Brown, A. E., and Foster, F. P. Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds. Further Clinical Observations, *J A M A* **111** 770 (Aug 27) 1938

119 Mansans, B. J. Tumors with Hollow Peduncle, *Nederl tijdschr v geneesk* **82** 5297, 1938

Microscopic examination of the tumor showed adenocarcinoma which had grown deep into the muscularis. The entire thickness of the muscularis, as well as the serosa, was found in the removed portion indicating that the surgeon had unwittingly removed a part of the intestinal wall. The author cites 2 cases of gastric tumor in which the wall of the stomach was drawn up into the tumor so that the growth appeared to have a peduncle. He points out the danger of attempting removal of such a tumor inasmuch as section of the apparent peduncle results in a fairly large opening, as noted in the aforementioned case. An additional point of caution which he might have stressed is the real danger of removing a rectal growth by simple cauterization.

GENERAL CLINICAL CONSIDERATIONS

Of general interest is the discussion by Bishop¹²⁰ on the relationship between gastroenterology and cardiology. He presents a summary of the points of confusion between cardiac symptoms and those due to diseases of the gastrointestinal tract. These are considered under several headings. First, he considers symptoms due to mechanical disturbances affecting the abdominal viscera, such as emboli or aneurysms, he then mentions the effect of pathologic conditions in the abdomen on the cardiovascular system and refers for example, to the effect of extreme flatulence on the activity of the heart of a susceptible person, he also emphasizes that overlapping areas of referred pain give diagnostic difficulty in differentiating between coronary disease, pericarditis and diseases of the gallbladder or stomach. He suggests that the presence of jaundice with its associated digestive disturbances may render the cardiovascular apparatus more easily subject to functional disturbances. Attention is called to the recognized important fact that patients having obvious coronary disease and gallstones are sometimes rendered free from cardiac symptoms after cholecystectomy. He also states, without detailed evidence, that in such cases the electrocardiogram may return to normal after cholecystectomy and further suggests that abnormal electrocardiographic changes in the presence of biliary tract disease may be due to associated vagal disturbances occurring with nausea and retching. The article contains nothing definitely new but brings up important clinical considerations that are worthy of repetition.

The ever increasing interest in the clinical and therapeutic implications of avitaminosis continues to be manifest. Among the numerous articles that have appeared on the protean manifestations of vitamin lack, several may be mentioned for their application to the problems of

¹²⁰ Bishop L. F., Jr. *Gastro-Enterology in the Practice of Cardiology*, J. A. M. A. **112** 33 (Jan 7) 1939

gastroenterology Among others, Musser and Sodeman¹²¹ review the gastrointestinal expressions of avitaminosis They maintain that sub-clinical expressions of scurvy, beriberi and rickets are common in the realm of alimentary tract disease Under three headings they discuss the specific deficiencies, chronic dietary deficiency and conditioned deficiency

Two authoritative articles by Cowgill¹²² should be read by all who are interested in the treatment of patients apparently suffering from the lack of vitamin B₁ In these articles Cowgill discusses the requirements of the normal adult and child, mother and infant, and pays particular attention to the loss of vitamin B₁ through excretory channels The last consideration is of extreme importance from the point of view of the widespread therapeutic use of thiamin chloride There is an appreciable loss of this substance in the presence of pronounced diuresis and also as a result of diarrhea In patients suffering from diarrhea the lack of this vitamin is frequently to be noted, and Cowgill's suggestion that adequate administration of vitamin B₁ under such circumstances can be obtained only by its parenteral use is timely and important

Further observations on the value of nicotinic acid have appeared during the year Of these, the most important are those of Spies and collaborators,¹²³ together with a similar article by Matthews¹²⁴ All these observers agree as to the remarkable efficacy of nicotinic acid in the treatment of pellagrous glossitis, stomatitis, vaginitis, urethritis and proctitis

Snell¹²⁵ discusses in an interesting fashion tropical and nontropical sprue on the basis of observations made on 46 patients Of these, 14 acquired sprue in the tropics, and 32 had what was diagnosed as non-

121 Musser, J H, and Sodeman, W A Gastro-Intestinal Expressions of Avitaminosis, *South M J* **31** 897, 1938

122 Dann, M, and Cowgill, G R Influence of Diarrhea on Vitamin B₁ Requirement, *Arch Int Med* **62** 137 (July) 1938 Cowgill, G R Human Requirements for Vitamin B₁, *J A M A* **111** 1009 (Sept 10) 1938

123 Spies, T D, Bean, W B, and Stone, R E The Treatment of Sub-clinical and Classic Pellagra Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, *J A M A* **111** 584 (Aug 13) 1938 Spies, T D, Cooper, C, and Blankenhorn, M A Use of Nicotinic Acid in the Treatment of Pellagra, *ibid* **110** 622 (Feb 26) 1938 Vilter, S P, Bean, W B, and Spies, T D Further Observations on Effect of 2,6-Dimethyl Dimicotinic Acid and Dimicotinic Acid on Pellagrins in Relapse and on Normal Persons, *South M J* **31** 1163, 1938

124 Matthews, R S Pellagra and Nicotinic Acid, *J A M A* **111** 1148 (Sept 24) 1938

125 Snell, A M Tropical and Non-Tropical Sprue (Chronic Idiopathic Steatorrhea) Their Probable Interrelationship, *Ann Int Med* **12** 1632, 1939

tropical sprue or idiopathic steatorrhea, acquired in central and north central states. In comparing the two groups Snell points out that so-called nontropical sprue differs from the tropical variety chiefly because of its extreme chronicity and the associated tendency toward disturbance of calcium metabolism and skeletal deformities. It is identical in all respects to the idiopathic steatorrhea cases of which have been reported in English and Scandinavian literature. The response to liver seemed best in those 20 patients whose condition most closely resembled tropical sprue, although in the remaining 12 occasional good results were obtained with adequate liver therapy. The report represents an excellent summary of an interesting and little known disease.

Brull and collaborators¹²⁶ also discuss nontropical sprue and report the results of a careful study of 4 cases of chronic diarrhea characterized by steatorrhea, a large deficit in intestinal absorption of calcium and phosphorus and resulting demineralization as evidenced by osteoporosis, hypocalcemia and tetany. The secondary clinical manifestations in these cases consisted of evidences of complex avitaminosis. The authors consider that the steatorrhea depends on B₂ (riboflavin) deficiency and think that the process of decalcification has the same fundamental origin. Melanoderma disappeared in these cases after treatment with lemon juice or solutions rich in water-soluble vitamins. Anemia was corrected by liver therapy, and disorders in phosphorus metabolism were treated by the administration of vitamin D. Any evidence of plasma vitamin A deficiency was treated by administration of this substance. The observations presented indicate that patients with this disease have a more or less deficient secretion of pepsin, hydrochloric acid, bile salts and lipase, but this is not particularly surprising in view of the known changes in the mucosa of the alimentary tract that take place in pronounced deficiency states. Brull points out that the entire symptomatic complex can be corrected by appropriate therapy but without counteracting the fundamental disorder, namely, a tendency to steatorrhea.

Of similar interest are several articles on the relationship between the alimentary tract and hemopoiesis. Brock,¹²⁷ in discussing intestinal strictures, gives a detailed description of 2 patients in whom megalocytic anemia occurred in association with intestinal strictures. The first patient had suffered for many years from a spruelike syndrome and at autopsy showed multiple intestinal stenoses. The second patient's anemia apparently followed tuberculous enteritis and responded to

126 Brull, L. Lambrechts, A., and Barac, G. Sprue non tropicale. Etude approfondie de quatre cas observes en Belgique. *Rev. belge sc. med.* **10** 457, 1938.

127 Brock, J. F. Intestinal Stricture and Megalocytic Anemia, *Lancet* **1** 72, 1939.

liver administered parenterally but not to liver given by mouth. It seems reasonable that in each patient the anemia developed because of lack of absorption of a hemopoietic factor by a damaged intestinal tract.

Sturgis and Goldhamer¹²⁸ also contribute observations on this subject. They present a rather interesting compilation of cases collected over eleven years and including various types of gastrointestinal lesions associated with macrocytic anemia. Of special interest are certain cases in which complete disappearance of the anemia followed relief of the intestinal condition, without the addition of any antianemic therapy. In another case macrocytic anemia improved with relief of chronic partial obstruction of the small bowel and recurred when this reappeared. These conditions do not represent true Addisonian anemia inasmuch as achlorhydria was frequently absent, and paresthesias and glossitis were uncommon. The authors observe that following gastric resection it appears that from two to five years are needed for the development of macrocytic anemia. They suppose that several factors are operative and that the development of anemia depends on the degree of gastric or intestinal impairment of function and on the amount of reserve erythrocyte maturing material stored in the liver and elsewhere, as well as possibly on the age of the patient and the presence of infection. It is possible that this apparent delay in the development of macrocytic anemia after subtotal gastrectomy, as noted by Sturgis, may account for the absence of reports in the literature describing this condition. Quite possibly such reports are premature, and further accounts will appear in future years as the performance of subtotal gastrectomy becomes more common.

An article by Meulengracht¹²⁹ based on a histologic study of the pyloric gland organ in pernicious anemia is of interest because of its divergence from the present day conception of this disease. Meulengracht's investigations were based on postmortem histologic examination of the stomach and duodenum in 8 cases of pernicious anemia. He demonstrated pronounced changes in the fundus, with atrophy of the glands and disappearance of special gland elements. Much less definite changes were noted in the pylorus, where the pyloric glands seemed to be well preserved, and no changes were observed in Brunner's glands. These pathologic observations are similar to those made by Faber and Block in 1900 but are at distinct variation with the observations of Brown published in 1934 as a result of autopsy studies in 151 cases proved to be cases of pernicious anemia. Brown's observations seemed

128 Sturgis, C. C., and Goldhamer, S. M. Macrocytic Anemia Other Than Pernicious Anemia Associated with Lesions of the Gastro-Intestinal Tract, *Ann Int Med* **12** 1245, 1939.

129 Meulengracht, E. Histologic Investigations on Pylorus Gland Organ in Pernicious Anemia, *Nord med tidsskr* **1** 11, 1939.

to coincide with the theory that changes in the mucosa of the pylorus and duodenum are the chief cause of pernicious anemia. The so-called pyloric organ consisting of Brunner's glands of the antrum and duodenum, has been believed to secrete Castle's 'intrinsic factor.' It is obvious that the two sets of observations are not entirely compatible, and Meulengracht discusses the possibility of correlating his results with the present conception of the genesis of pernicious anemia. He suggests that the disease results from a failure of the interaction between the intrinsic and the extrinsic factor which originates a third principle or liver factor and that such a failure must be ascribed to disturbances of the small intestine. The discussion is largely of academic interest, but it must be admitted that Meulengracht's suggestion may have some bearing at least on the macrocytic anemias referred to in the preceding articles.

Recognition of the role played by the autonomic nervous system in the production of colonic symptoms is evidenced in the work reported by Leriche and collaborators¹³⁰ on the treatment of spastic colitis. The authors report their experience in the treatment of certain forms of spastic colitis by infiltration of the lumbar sympathetic and section of the splanchnic nerves. Nine patients were so treated. Usually the pain ceased after the first injection into the left lumbar sympathetic trunk and after a second injection constipation was relieved to the extent that daily dejections were obtained without the use of laxatives. In a few cases of persistent right-sided pain it was necessary to infiltrate the lumbar sympathetic nerves on the right side. In a patient who was reexamined eighteen months after three infiltrations had been performed although the symptoms had disappeared, roentgen evidence of spasticity in the colon persisted. The injections appeared to have modified the functional or neurogenic element without producing any anatomic changes in the intestine. No explanation is given of this apparent discrepancy. Another patient with intractable constipation noted the appearance of daily bowel movements without the use of laxatives seven days after an operation which consisted in resection of the left splanchnic nerve and first lumbar ganglion, and the improvement continued during the period of sixteen months' observation. The authors call attention to the need for careful study in such cases, inasmuch as not all patients can be benefited by such procedures. The findings reported by these investigators are of interest, inasmuch as measures tending to block parasympathetic activity are the usual ones employed to relieve so-called spastic colitis. Surgical revision of the sympathetic nerves has been used in the past only to permit more normal

¹³⁰ Leriche, R., Kunlin, J., and Froehlich, F. Infiltrations novocamiques du sympathique lombaire et section du splanchnique dans certaines colites spasmodiques, *Progres med* 67 11, 1939.

peristalsis by removing anything that inhibits parasympathetic activity. It is probable that the relief obtained in the cases described by Leriche and his collaborators was due to interruption of sensory impulses carried over sympathetic fibers rather than to any interference with abnormal motor activity.

In this connection an article by Wakefield and C W Mayo¹³¹ is of interest. These authors discuss the functional or sociologic disorders of the colon, a rather remarkable subject for joint discussion by a psychiatrist and a surgeon. They point out that the vast majority of colonic disorders are undoubtedly functional, although many of them are of sufficient severity to warrant surgical intervention. It is to this group that so well known a surgeon as Mayo and his associate call attention. The article is well worth reading, not for the presentation of new material, but for a rational and proper approach to the consideration of psychosomatic disorders.

Wilbur and Mills,^{1,2} also of the Mayo Clinic, likewise discuss functional digestive disturbances in a group of 354 patients. The article is of particular interest as it points out some mistakes that have been made in the diagnosis of functional indigestion. Actually, accurate diagnoses were made in 85 per cent of the cases, due to the fact that care was taken in establishing them. The patients were reexamined at an average of seven years after their first admission to the clinic, and at the second examination 39 were found to have organic disease of the gastrointestinal tract. Nineteen of these had duodenal ulcers, which appeared to be the commonest source of error. Other diagnoses were gastric ulcer, gallbladder disease, cancer of the stomach and, in addition, extraalimentary tract disease (12 cases), such as pernicious anemia, heart disease, hyperthyroidism and others. The article is of value because it demonstrates the possibility of establishing a correct diagnosis of functional indigestion if sufficient care is used. It also demonstrates the necessity of following "functional" conditions that do not show adequate response to therapy.

Klingman¹³³ also has written a rather interesting report on the treatment of neurogenic megacolon by drugs. He attempts to differentiate acquired megacolon into two types: one which he calls rectosigmoidal achalasia and a second in which the parasympathetic motor function fails to act effectively above the rectosigmoid. In the first type the failure of the rectosigmoid to relax is thought to be due to over-

131 Wakefield, E G, and Mayo, C W. Functional or Sociologic Disorders of the Colon, *J A M A* **111** 1627 (Oct 29) 1938.

132 Wilbur, D L, and Mills, J H. How Accurate Is the Diagnosis of Functional Indigestion? *Ann Int Med* **12** 821, 1938.

133 Klingman, W O. Treatment of Neurogenic Megacolon with Drugs, *J Pediat* **13** 805, 1939.

activity of sympathetic inhibition, with resulting spasm, or failure of the parasympathetic nervous system properly to inhibit the rectosigmoidal apparatus. The author chooses syntropan as the most effective drug to paralyze the parasympathetic nerves. Barium sulfate enema studies seem to indicate that in rectosigmoidal achalasia there is marked delay in the emptying of the rectosigmoidal apparatus. Where there is deficient motor function (parasympathetic nerves) of the colon above the rectosigmoid a barium sulfate enema demonstrates good emptying of the lower part of the colon but retention of barium sulfate in the upper part. When roentgen examination establishes that the rectosigmoidal apparatus is functional Klingman tries prostigmine. If normal function cannot be demonstrated he advocates the use of amphetamine sulfate (benzedrine) or syntropan and if there is no response to either of these methods he advises lumbar ganglionectomy and presacral resection.

Redon¹⁴ reports a case of definite clinical interest because of the unequivocal nature of the specific findings. The patient presented severe pain on the right side of the abdomen with moderate elevation of temperature. An emergency diagnosis of appendicitis was made, which was subsequently rejected by the surgeon, who considered the possibility of acute intussusception. At exploration the ileocecal region showed a sparkling edematous mass and no other abnormality. An immediate diagnosis of Quincke's edema was made, and histologic examination of the appendix, which was removed, showed no sign of an inflammatory process. The diagnosis should have been suspected before operation because of the history which included frequent urticarial crises, especially after the ingestion of fish, and the added statement that he had eaten fish and mussels just prior to the attack. The chief interest in the report is that it furnishes clear evidence of visceral urticaria as an explanation for a certain type of obscure abdominal symptoms.

Because of the increasing awareness that amebic infestation of the intestinal tract is not uncommon in this country, the roentgenologic study of amebiasis by Gómez¹⁵ is worthy of attention. The author describes his findings in 10 patients with chronic amebiasis with digestive symptoms but without diarrhea and in 25 patients with acute or chronic amebiasis with active diarrhea. In each instance a barium sulfate meal and barium sulfate enemas formed the basis of the roentgen studies. Delay in the passage of barium sulfate from the stomach was the rule, but the duodenum and ileum appeared almost uniformly nor-

134. Redon H. Crise d'œdème de Quincke visceral simulant une appendicite aiguë, *J de chir* 53: 360, 1939.

135. Esguerra Gomez, G. La radiología de la amibiasis, *Rev. Fac. de med., Bogota* 7: 45, 1938.

mal The cecum and especially the transverse colon showed increased segmentation of varying degrees, and the caliber of the colon was distinctly diminished There was uneven distribution of barium sulfate through the colon, some of the colon appearing apparently normal, with deformities being noted at irregular intervals These deformities, however, characteristically remained the same in a given patient and presented the general aspect of lesions associated with ulcerative colitis

Two articles relative to giardiasis are of interest Veghelyi,¹³⁶ of Budapest, in an examination of 1,391 children between the ages of 2 and 17, found evidence of giardia (lamblia) infestation in 155 Complete examinations were performed in 144 of these children, 32 gave evidence of other diseases, 20 had a positive tuberculin test, and 92 showed no evidence of any other disease The last group was compared with a group of healthy children of the same age in regard to the presence of symptoms referable to the digestive tract Some of the children who showed evidences of giardia infestation had no symptoms or approximately none In more than half of the children, however, gastrointestinal complaints, such as anorexia, headache, dizziness and abdominal pain were present At times, intense acute pain was noted over the cecum, independent of meals and occurring in cramplike attacks Mucus, pus and blood had been seen in the feces in one fourth of the infested group, two thirds had irregular bowel movements Examination of the lungs, heart and kidneys revealed no abnormalities in the entire group A more striking difference between the healthy and the infested children was that 79 of the latter were underweight There were no hepatic disorders, and the author feels that the symptoms and evidences of undernutrition were fundamentally due to an impairment of the absorption of food from an irritated alimentary tract In 29 of 32 children the symptoms disappeared completely after treatment with acetarsone Such treatment was followed by definite improvement in the blood and gain in weight Unfortunately, no mention is made of the complete and lasting disappearance of Giardia from the stools The article is well prepared, however, and the comparison with a group of normal controls presents fairly convincing evidence that giardiasis may be responsible for symptoms referable to the alimentary tract

De Muro¹³⁷ discusses the treatment of patients with giardiasis and reports some results obtained in 15 who were treated with atabrine, introduced for the treatment of this condition by Galli-Valerio in 1937

¹³⁶ Veghelyi, P. Giardiasis in Children, *Am J Dis Child* **56** 1231, (Dec) 1938

¹³⁷ de Muro, P. Atebrinbehandlung bei Giardiasis (Lambliasis), *Deutsche med Wchnschr* **65** 262, 1939

Of the 15 patients, 8 showed chronic colitis and 2 proctitis, and 5 were said to have symptoms referable to the intestinal and biliary systems. The atabrine was administered in the same fashion as to patients with malaria over a period of five days. Examination of the stools and duodenal contents in 13 cases gave negative findings for *Lambia* after five days of treatment. The intramuscular administration of atabrine cleared the stools of *Giardia* but did not cause their disappearance from the duodenal contents. In each instance the disappearance of the parasites was followed with great improvement in symptoms and improvement in the character of the stools.

Reports have appeared from two groups of investigators on the value of phenolphthalein administered orally as a test of gastrointestinal ulceration—a procedure introduced by Woldman a year ago. Kremer, Shore and Wiesel¹³⁸ administered the drug orally to 137 patients and report the test correct for 56 per cent of them showing gastrointestinal disease with correct negative results for 79 per cent. Of 69 patients studied simultaneously by other routine procedures, the test was correct for 72 per cent. Patients with cardiovascular disease, infections, blood dyscrasias and certain other conditions without obvious disease of the digestive tract gave a number of falsely positive results. The authors conclude that the test may be valuable as an adjunct to other diagnostic methods but that more must be learned of its use before it can be considered at all reliable.

Confirmation of this skeptical point of view is found in a report by Steigman and Dymewicz.¹³⁹ These authors state that free phenolphthalein generally appears in the urine whenever the quantity of conjugated phenolphthalein in any one specimen exceeds 5 mg. per hundred cubic centimeters of urine. In some abnormal conditions such as cardiac or renal disturbances and diseases of the blood free phenolphthalein may appear at an even lower level. In a fair proportion of patients with nonulcerous diseases and of normal persons such a concentration is reached after ingestion of the test dose of phenolphthalein devised by Woldman; hence the appearance of free phenolphthalein in the urine cannot be considered as diagnostic evidence of ulceration in the intestinal tract.

Although any attempt to review the literature on infectious diseases involving the gastrointestinal tract is beyond the scope of this paper, it may be proper to mention the relatively frequent reports that have

138. Kremer, D. N., Shore, P. D., and Wiesel, B. H. Phenolphthalein as a Test in Gastro-Intestinal Disease, *Am. J. Digest. Dis.* **6**: 192, 1939.

139. Steigman, L., and Dymewicz, J. M. Urinary Elimination of Free Phenolphthalein: No Test for Gastro-Intestinal Ulceration, *Am. J. Digest. Dis.* **6**: 120, 1939.

appeared on outbreaks of bacillary dysentery in other than subtropical areas Bowes¹⁴⁰ gives an interesting account of Sonne dysentery due to milk, which involved 59 of 106 households in a given area in England Blatt and Shaw¹⁴¹ record a study of 356 children with bacillary dysentery from the children's division of the Cook County Hospital in Chicago Another article by Lammerts van Bueren and de Haas,¹⁴² although it comes from Batavia, is of some interest inasmuch as these writers report that among 400 children with bacillary dysentery observed at the Children's Clinic there were 160 nurslings, 11 of whom were less than 6 months old The authors conclude that bacillary dysentery may attack children even during the first three months of life irrespective of whether they are bottle or breast fed, they comment on the fact that the feces of affected nurslings are usually less dysenteric in character than those of older children with this disease

A possible contribution to the solution of the problem of local tissue immunity is found in an article by Torikata and Imaizumi¹⁴³ on local intestinal immunity These authors administered daily oral doses of heat-killed colon bacilli to guinea pigs, with control immunization of other animals by routine subcutaneous methods Ten days after the final administration of the vaccine, serums were withdrawn from each group of animals, and expressed tissue juices were prepared from the walls of the intestinal tract Titrations of these serums and tissue juices showed an 80 to 100 per cent increase in opsonic titer of the intestinal tissues as a result of the oral administration of vaccine, but only a 10 to 20 per cent increase in the blood serum In the control group there was a 76 to 100 per cent increase in the opsonic index of the blood stream, with less than half of that percentage in the intestinal tissue juices The authors conclude that oral immunization with heat-killed *Bacillus coli* is effective in rendering the intestinal tract refractory to homologous infections long before effective humoral or somatic immunity is produced An additional comment in this article quite properly points out the potential value of such studies, which should encourage further investigation relative to the route of administration of vaccines

140 Bowes, G K Outbreak of Sonne Dysentery Due to Consumption of Milk, *Brit M J* **1** 1092, 1938

141 Blatt, M L, and Shaw, N G Bacillary Dysentery in Children Study of Three Hundred and Fifty-Six Cases from the Children's Division in the Cook County Hospital, Chicago, *Arch Path* **26** 216 (July) 1938

142 Lammerts van Bueren, B and de Haas, J H Bacillary Dysentery in Young Nurslings, *Maandschr v kindergeneesk* **7** 461, 1938

143 Torikata, R, and Imaizumi, M Zum Unterschiede zwischen der Injektions- und der oralen Immunisierung, *Ztschr f Immunitatsforsch u exper Therap* **94** 342, 1938

In the field of preventive medicine, two recent articles seem to be of extreme importance. Trask and his associates¹⁴⁴ made a very careful study of a small epidemic of poliomyelitis. Since the original observations in 1912 by Kling and his collaborators, few investigators have successfully isolated the virus of this disease from the human intestinal tract, although one brief mention was made by Harmon of a successful attempt in 1937. Trask and associates isolated the virus from the stools three times in a single case. The child whose stools contained the virus was ill for only three or four days, but the virus persisted in the stools for at least twenty-four days from the onset of this mild illness. Although the authors do not imply that the virus necessarily enters the body by way of the gastrointestinal tract, they point out the seasonal prevalence of poliomyelitis, which like typhoid and dysentery, occurs largely in the summer. They also mention a fact that is not so well known, namely, the presence of lesions in the intestinal tract. The writers suggest that during an epidemic of poliomyelitis the common mild and often unrecognized forms of the disease may be responsible for a high degree of pollution of the sewage with poliomyelitis virus. Kramer, Hoskwith, and Grossman¹⁴⁵ report the isolation of the virus from the upper intestinal segment of a monkey killed at the height of the disease. The virus apparently is able to withstand acidity, and this finding emphasizes the extreme importance of a proper disposal of feces from patients suffering from poliomyelitis, particularly in small communities with inadequate sewage disposal facilities.

144 Trask, J. D., Vignec, A. J., and Paul, J. R. Poliomyelitis Virus in Human Stools, *J. A. M. A.* **111**: 6 (July 2) 1938.

145 Kramer, S. D., Hoskwith, B., and Grossman, L. H. Detection of the Virus of Poliomyelitis in the Nose and Throat and Gastro-Intestinal Tract of Human Beings and Monkeys, *J. Exper. Med.* **69**: 49, 1939.

Book Reviews

The Endocrine Glands By Max A Goldzieher, M D, Endocrinologist, Gouverneur Hospital and Brooklyn Women's Hospital Price, \$10 Pp 916, with 271 illustrations New York D Appleton-Century Company, Inc, 1939

As stated in the preface, the aim of the author was to provide a "book which discusses with equal thoroughness and on the basis of first hand information both the theoretical and practical aspects of endocrinology" The first section is concerned with general principles of endocrinology and the relation to other fields. Succeeding sections deal in turn with the individual endocrine glands, including the thymus and the pineal body. Each of these sections includes brief chapters on historical material and on the embryology, anatomy, histology and physiology of the gland in question. These are followed by a chapter on morbid anatomy. Longer chapters discuss the various clinical disorders, their classification, etiology, pathogenesis, diagnosis and therapy. References to the literature, conveniently placed at the end of chapters or subjects, are liberally supplied. A large number of photographs of patients and of histologic sections are provided.

The author shows a commendable reluctance to attribute endocrine functions to the thymus gland. A creditable case is made in support of the recent view that Cushing's syndrome is related more to adrenal than to pituitary hyperfunction. Various forms of adrenal insufficiency receive considerable attention. However, in many instances the cautious reader will reserve his opinion regarding the efficacy claimed or implied for some of the forms of endocrine therapy.

A commendable attempt is made throughout this book to correlate clinical and physiologic knowledge. The well informed reader will criticize or desire to qualify numerous statements, interpretations and implications made by the author. This is true of any book dealing with a subject concerning which more is to be learned than is known. The book will serve as a good text if the limitation of existing knowledge is kept in mind and if some of the opinions and the therapeutic suggestions of the author are not taken too literally and considered as established.

Cause and Prevention of Disease By William Harvey Perkins, Professor of Preventive Medicine, Tulane University of Louisiana Price, \$7.50 Pp 713, with 1 diagram and many tables Philadelphia Lea and Febiger, 1938

The author has gathered in a single volume a great many facts which bear on the cause and prevention of disease.

Various direct or indirect causes are discussed under six headings. Heredity, nutrition, chemical agents, physical agents, animate agents and psychobiologic or biosocial factors are each given credit, either alone or in combination, for causing illness. The author's method of approach to discussing the cause of disease is to arrange these different agents in various classes according to their characteristics and to their effect.

The preventive measures that may be employed against these agents are considered collectively and individually. There is a tendency toward repetition, but, on the whole, the work is an excellent reference book for physicians and students who wish to obtain a quick resume of a particular subject in the field of preventive medicine.

From the standpoint of a textbook for medical schools, the book does not fully meet the practical needs of the student. It does not cover completely the practical application of technical methods in the field of public health. In certain parts of the text the style and phraseology are involved, making rapid assimilation difficult. The proportionate allotment of space for any subject does not always

coincide with its relative importance, for instance, a disproportionate amount of space—one quarter of the book, is devoted to a detailed account of the exogenous chemical agents and their toxicology. However, the author is to be congratulated on his compilation of a condensed but inclusive review of so difficult a subject as the causes of disease and the methods of prevention.

On the Stability of Transfused Erythrocytes By H. J. N. Dekkers. Pp. 104. Amsterdam: Scheltema & Holkema, 1938.

The estimations of the duration of life of the erythrocyte vary—with the author and the method of approach employed—from fifteen to two hundred days. Heretofore practically all methods had to be limited to indirect procedures. The finding of the existence of blood groups M and N (Landsteiner and Levine, 1927) made possible the direct identification of transfused compatible red blood cells. The author found the average time for existence of erythrocytes after transfusion of 500 cc. of blood to be seventy-five and one-half days by microscopic evidence of heteroagglutination and fifty-four and one-half days by macroscopic evidence. The results of more than one hundred transfusions could be traced until after the disappearance of all the cells of the donor in 12 cases only. Four additional patients were traced forty-two to seventy-six days after the transfusion, at which time transfused erythrocytes were still present. Light patients with secondary types of anemia in whom disease leading to increased destruction of erythrocytes can be supposed to have been absent showed the presence of transfused cells after fifty-nine to ninety-five days. The maximal erythrocytic survival in 1 case of toxemia of pregnancy with uremia and solution of the placenta was forty-five days; in 1 case of staphylococcal sepsis it was forty days; in 1 case of subacute myeloid leukemia it was twenty-three days; and in 1 case of pernicious anemia it was seventy-six days (thus being within normal limits).

Internal Medicine: Its Theory and Practice in Contributions by American Authors. Edited by John H. Musser, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine, Senior Visiting Physician to the Charity Hospital, New Orleans. Third Edition. Price \$10. Pp. 1428 with 18 tables and 37 illustrations. Philadelphia: Lea and Febiger, 1938.

The first edition of this textbook appeared in 1932. The *ARCHIVES* liked it, complimented it and at the same time proved a good fortune-teller. The *ARCHIVES* said: "On the whole, the new textbook is admirable. Teachers, students and practitioners will enjoy it, not only because it is well and clearly written, but also because it opens up the vast field of medical knowledge in a simple, interesting and engaging manner."

That teachers, students and practitioners have enjoyed the book is obvious, for only a popular, widely read text could make necessary three editions in six years.

Osler's "Practice of Medicine" accomplished the same feat. The first edition of Osler's text appeared in 1892, the third in 1898. In those days, apparently, medical knowledge developed at about the same pace as nowadays, the third edition of Osler's book was 131 pages longer than the first, the third edition of Musser's book is 112 pages longer than the first.

In the preface to the latest edition Musser states that his "Internal Medicine" has undergone careful scrutiny and extensive revision since its birth. New knowledge and ideas have been incorporated in the 1938 model, new concepts of pathologic physiology are described, and new forms of therapy are discussed. On the whole, once again the *ARCHIVES* compliments the book. It is up-to-date. It continues to open up the vast field of medical knowledge in a sensible, interesting and engaging manner. It is certain to be popular.

Progressive Relaxation By Edmund Jacobson, A M, Ph D, M D Second Edition Price, \$5 Pp 493, with illustrations Chicago The University of Chicago Press, 1938

The value of rest as a therapeutic measure has long been appreciated, but the study of relaxation from a scientific standpoint is a comparatively new venture ably undertaken by the author of this book

The importance of "neuromuscular hypertension" in many organic and functional states is discussed, and the efficacy of relaxation in the treatment of these conditions is indicated The technic of progressive relaxation which is used by the author is described clearly and in detail An interesting series of experiments is reported in which the effect of relaxation on the knee jerk is recorded graphically A study of the relation of mental processes and of emotions to muscular tension is presented, together with a method of measuring neuromuscular processes in mental activities Apparatus and procedures are described which may be used to measure in electrical terms all degrees of muscular contraction These procedures may be of clinical use in the accurate determination of tension in patients who exhibit this symptom A complete bibliography is included at the end of the book

This work is an original and noteworthy contribution to a new field of investigation which should be of interest to the neuropsychiatrist, the physiologist, the internist and all others who deal with problems of the tense patient

Survey of Carbon Disulphide and Hydrogen Sulphide Hazards in the Viscose Rayon Industry Bulletin 46, Division of Occupational Disease Prevention, Commonwealth of Pennsylvania, Department of Labor and Industry, 1938

This bulletin of 69 pages deals with a specific industrial poison in the rayon industry Each aspect of this occupational disease problem is discussed in detail by a writer especially qualified by training and experience The authors include members of the Pennsylvania Department of Labor and Industry, the United States Department of Labor and the faculties of the University of Pennsylvania and the Pennsylvania State College

The pamphlet is well written and well arranged Its publication is timely and will be welcomed by all those interested in the field of industrial health One regrets the apparent political necessity of the frequent repetition of names of politicians in the first eight pages

A Historical Chronology of Tuberculosis By Richard M Burke Price, \$1.50 Pp 81, with 1 chart Springfield, Ill, and Baltimore Charles C Thomas, Publisher, 1938

From the beginning of history to 1938, the author outlines by brief statements the development of knowledge of tuberculosis Under the year 1885, for example, among several items, one reads that "Edward Livingston Trudeau (1847-1915) founds Adirondack Cottage Sanatorium at Saranac Lake, New York Employs bed rest in the presence of symptoms He becomes patron saint of the American consumptive" In sixty-three pages of this sort of treatment a vast amount of ground is covered, and every physician should find this compendium indispensable Finally, there are indexes of names and subjects and a large chart showing in tabular form the most important matters dealt with in the text

Les dystrophies dentaires de la syphilis héréditaire By Lucien Lebourg Price, 38 francs Pp 164 Paris Gaston Doin & Cie, 1939

This is an excellent monograph on the changes that take place in the teeth of the child or adult who has inherited syphilis The book is of considerable cultural interest to the physician and undoubtedly will be of great practical interest to the dentist

News and Comment

New York Diabetes Association, Inc—The New York Diabetes Association Inc., offers three grants of up to \$500 each for research in diabetes. These grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus and materials which are ordinarily a part of laboratory equipment. The researches must be carried out in Greater New York, although the persons engaged in them need not be residents of Greater New York.

Letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the proposed research, the size of the grant requested and the specific use of the money to be expended. It is highly desirable to include a list of men with whom the applicant has been and is associated who would be willing to give letters of recommendation and sponsor the applicant. Applications should be mailed to the Committee on Research, New York Diabetes Association, Inc. 22 East Fortyeth Street, New York.

Applications will be received up to Nov. 1, 1939.

Seventh International Congress on Rheumatism—The subjects to be discussed at the Seventh International Congress on Rheumatism, to be held in New York, Philadelphia and Boston, June 1 to 10, 1940 will be infection, nutrition and treatment. Free lectures will be given afterward.

Besides a visit to the World's Fair, which it is expected will still be open, the American Medical Association has organized a scientific exhibit in the field of medicine, which will in itself undoubtedly be worth a visit to the United States.

Further information regarding this congress may be procured from the International Bureau, Keizersgracht 489, Amsterdam, Netherlands.

Obituaries

WILLIAM J MAYO, M D

1861-1939

Dr William J Mayo was one of the great medical figures of these times. Every one knew his name. His influence on present day medicine as well as surgery is perceptible in many ways.

Dr Mayo was a great clinical teacher. He was lukewarm to undergraduate teaching, feeling that what could be taught of medicine to undergraduates was, on the whole, elementary and that in the making of the finished product, particularly in surgery systematized post-graduate training was essential.

His method of teaching was entirely personal. He had little confidence in pedagogic formalities. He believed that the most effective way to teach was by the method of learning. He himself always was eager to learn, and so it was that he worked every day in the clinic, seeing patients, rubbing elbows with his students and, by force of example, setting them a pace to do better work and thereby get a better education.

He felt that experience was the greatest teacher of all. This was true in his case. He was familiar with every phase of disease.

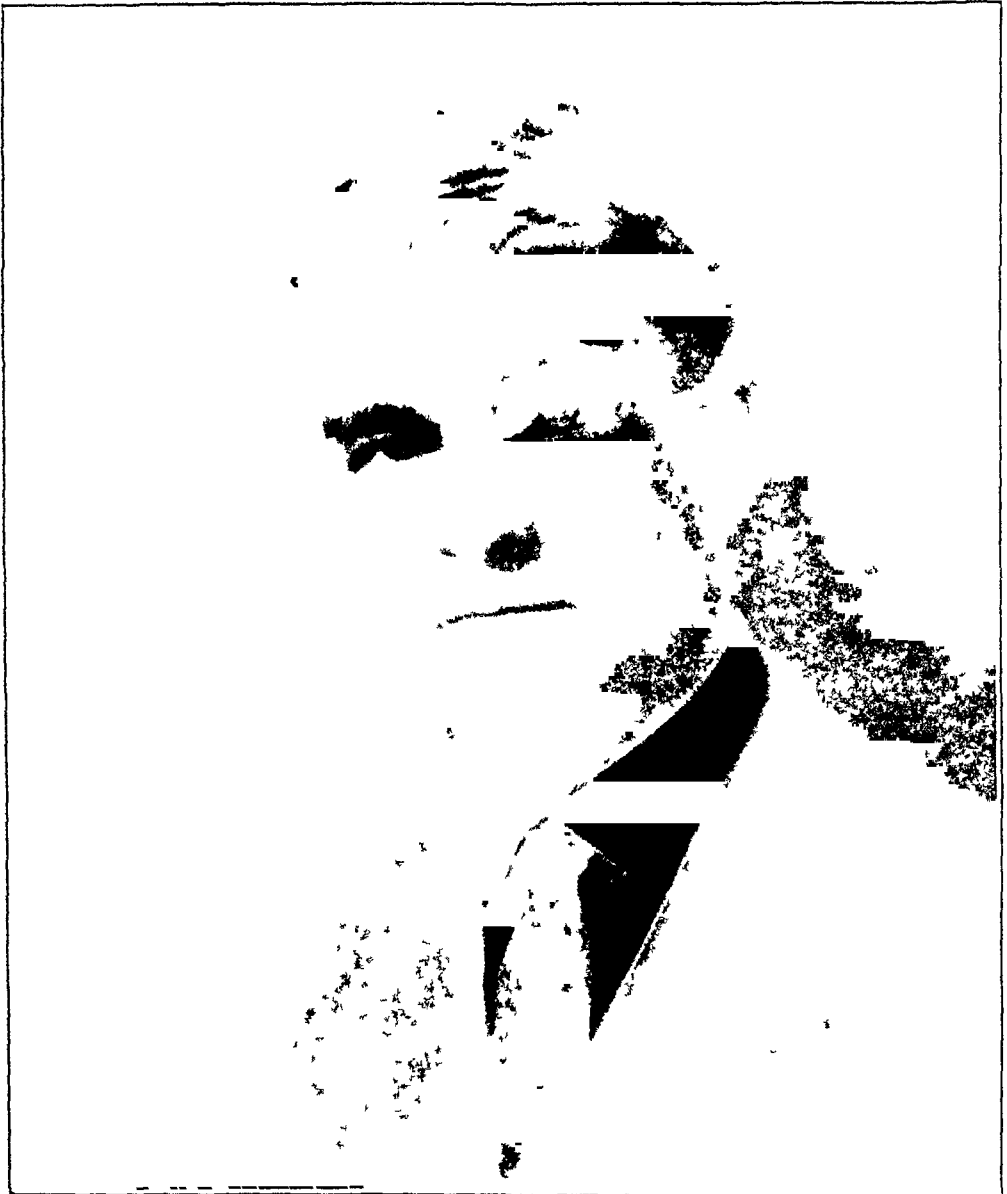
Dr Mayo believed in imaginative persons. That was one of the reasons why he liked to be surrounded by young men. He felt that as one grew older one tended to become conservative, gaining, perhaps, in judgment but, on the other hand, losing in ability to look ahead. He dreaded anything static.

One day on the Mississippi River he remarked, as he watched the current flow past, that American medicine is much like a river. Some of today's medical schools with their elaborate equipment are like bits of wood caught in an eddy. They go round and round, stirring up a certain amount of foam but making no headway. On the other hand, other schools less cumbersome are being so adroitly piloted as to avoid the eddies and are going downstream serenely. He feared medical complacency. He wished to see medical knowledge advance steadily.

He believed in the American Medical Association. He said that all physicians belonged to a common brotherhood. Some, by the grace of God, were more fortunate than others, and those who could should work for the benefit of the rest. He felt that the way to be of greatest

service to all is through loyalty to the Association. Of his various honors he prized the Presidency of the American Medical Association among the highest.

He was no showman. He believed, however, that one should learn how to talk without notes or hesitation, briefly and clearly, and should



WILLIAM J MAYO, MD
1861-1939

know how to assemble material in readable form, well illustrated and well expressed. The result of this discipline has been obvious. A medical paper from the Mayo Clinic almost invariably is well done. A speaker from the clinic almost invariably is interesting and instructive.

Dr Mayo was not particularly concerned over the bugbear of socialized medicine. He took pride in being an American citizen and had unbounded confidence in the country's future. He thought that the ordinary person wished to pay for medical service and would do so gladly if the cost could be kept within reasonable limits. He strove to offer to his patients the highest type of service at moderate cost. This became the fundamental policy of the clinic.

Dr Mayo believed that the Mayo Clinic belonged to the patients. It seemed to him that the wisest way through which to safeguard their future health was by investing in postgraduate medical education the money which they had placed in his hands. With this concept the Mayo Foundation was first established and since has grown into a great postgraduate medical school.

Persons from all parts of the world have been trained in the Mayo Clinic. In nearly every medical center some one from the Mayo Clinic is at work, trying as bravely as he can to carry forward Dr Mayo's precepts. This fact as well as any other, epitomizes Dr Mayo's work. He was proud of even the humblest accomplishments of any of those who had worked under him. He was a model teacher, not self seeking but content to let his pupils harvest the fruits of his planting.

CHARLES H MAYO, M D

1865-1939

Dr Charles Horace Mayo died in a Chicago hospital in May 1939, known and mourned perhaps even more widely than his equally distinguished brother. He was a human person, Dr Charlie, and had



CHARLES H MAYO, M D

1865-1939

the gift of making lasting friends. He had the gift and made the effort. The world's most famous surgeon, in the golden age of surgery, was never too fatigued to include friendliness in his self-imposed prescription for medical care.

In the early annals of Rochester Dr Charlie was the man who tried everything first. He operated on the first goiter among the Mayo

patients. He experimented with mica plates and the first x-ray apparatus. In the original building at St. Mary's Hospital an elevator is still in use which he planned and installed. He was forever on the watch for some new door to open. And each time he opened a door it was with some specific patient in mind.

He was a homely man in the classic sense. His accumulation of academic robes from institutions of learning the world over attests his high position in the professional world; he served as president to almost every medical and surgical society of which he was a member. And yet he served as health officer to the little city of Rochester at about the same time that he was President of the American Medical Association, and there is the perfectly authenticated story of his polishing the boots of a British guest. Dr. Mayo knew, as the guest did not, that household servants in America do not polish vagrant shoes left outside of bedroom doors. Visitors present at the University of Edinburgh when that institution honored him with their most distinguished degree reported that the traditionally solemn audience shouted with laughter at his acceptance speech. They were listening to words of dry humor, spoken in the accent of the American Middle West, and they sensed it to be the humor of another Mark Twain or a Will Rogers.

Had his been a less dynamic personality he might have spent his life playing second fiddle to his brilliant elder brother, but fortunately they complemented rather than obscured each other. It was Dr. Charlie's privilege to use his gifted hands to alleviate human suffering and his inventive mind to experiment with new methods of surgery. But it was a happy coincidence that one born with such gifts should also have been endowed with such unusual human understanding and sympathy to help when fingers and invention failed.

OPTIMUM TIME FOR ADMINISTRATION OF PROTAMINE ZINC INSULIN

MORTON F. MARK, M.D.

NEW YORK

Hagedorn, Norman Jensen, Krarup and Wodstrup,¹ who were the first to use protamine insulin, gave in most of their cases a dose of protamine insulin in the evening and one of regular insulin in the morning. The addition of zinc to protamine insulin by Scott and Fisher² prolonged the action of the new preparation considerably, so that a single injection a day was sufficient to control the diabetes in a large percentage of cases. Sprague and his associates³ adopted the procedure of giving the single dose of protamine zinc insulin early in the morning, and their method was soon followed by most investigators (Campbell and his associates,⁴ Joslin,⁵ Rabinowitch⁶ and others).

In previous studies (Mosenthal⁷ and Mark, Sackey and Mosenthal⁸) in which a single dose of protamine zinc insulin was administered at 6 or 7 a. m., it was found that there was a rise of the level of sugar

From the Department of Metabolism, Sea View Hospital and New York Post-Graduate Hospital, Dr. Herman O. Mosenthal, Director.

1 Hagedorn, H. C., Norman Jensen, B., Krarup, N. B., and Wodstrup, I. Protamine Insulinate, *J. A. M. A.* **106** 177-180 (Jan. 18) 1936.

2 Scott, D. A., and Fisher, A. M. Studies on Insulin with Protamine, *J. Pharmacol. & Exper. Therap.* **58** 78-92 (Sept.) 1936.

3 Sprague, R. G., Blum, B. B., Osterberg, A. E., Kepler, E. J., and Wilder, R. M. Clinical Investigations with Insulin Protamine Compound, *Proc. Staff Meet., Mayo Clin.* **11** 257-258 (April 22) 1936.

4 Campbell, W. R., Fletcher, A. A., and Kerr, R. B. Protamine Insulin in the Treatment of Diabetes Mellitus, *Tr. A. Am. Physicians* **51** 161-173, 1936.

5 Joslin, E. P., Root, H. F., Marble, A., White, P., Joslin, A. P., and Lynch, G. W. Protamine Insulin, *Tr. A. Am. Physicians* **51** 174-187, 1936.

6 Rabinowitch, I. M., Foster, J. S., Fowler, A. F., and Corcoran, A. C. Clinical Experiences with Protamine Zinc Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, *Canad. M. A. J.* **35** 239-252 (Sept.) 1936.

7 Mosenthal, H. O. Protamine Zinc Insulin, *J. A. M. A.* **110** 87-90 (Jan. 8) 1938.

8 Mark, M. F., Sackey, M. S., and Mosenthal, H. O. Protamine Zinc Insulin in the Treatment of Diabetes Complicated by Tuberculosis, *Quart. Bull., Sea View Hosp.* **2** 357-362 (July) 1937.

in the blood after each meal and that the lowest determinations were those obtained at 3 or at 6 a m. At that time it was felt that the reason for the low values for sugar during the early morning hours was not that the maximum effect of the insulin occurred twenty-one to twenty-four hours after injection but rather that food was withheld during the night. Obviously, it would be a fortunate circumstance if the low blood sugar values during the night did represent the maximum effect of the insulin at that time, since, if this were the case, the early morning hypoglycemic reaction and the postprandial hyperglycemia that so commonly occur in severe diabetes could be eliminated by changing the time of administration of the insulin.

Lawrence and Archer,⁹ who, like most investigators, found that many patients with severe diabetes could not do well with a single dose of protamine zinc insulin in the morning, reported satisfactory results in 6 cases when the insulin was given at bedtime. Their explanation was that when the insulin was administered at night, its minimum action coincided with the hours of sleep and its maximum with the intake of the day's food. They, however, said they believed that most patients obtain better control when protamine zinc insulin, with or without the addition of a dose of regular or soluble insulin, is given before breakfast. Joslin¹⁰ has quoted a personal communication from Himswoorth, who claimed to have obtained excellent results by administering protamine zinc insulin at 11 p m. It appeared that the food was far better utilized the following morning than if the protamine zinc insulin were given before breakfast.

As my associates and I were unable to observe any striking change in the character of the control of diabetes in a few cases by altering the time of administration of protamine zinc insulin from morning to night, the present study was carried out in order to arrive at a definite conclusion as to the optimum time of day for the injection.

MATERIAL

The work was done in the metabolic service at Sea View Hospital on 6 patients who, in addition to diabetes, had pulmonary tuberculosis. Since these patients were hospitalized for a long period, they could be kept under constant and careful observation. In order to eliminate the changes incident to variations in body temperature, only afebrile patients were selected.

The patients were on a diet having a carbohydrate value of 150 to 200 Gm. Four meals a day were given (at 7:30 a m., 11:30 a m., 4:30 p m. and 8:30 p m.) with the carbohydrate divided so that 25 per cent was allowed at breakfast and at lunch, 35 per cent at dinner and 15 per cent at 8:30 p m. Determinations of the blood sugar value were made at frequent intervals throughout the twenty-four hours by the capillary method of Folin-Malmros. For 3 of the

9 Lawrence, R. D., and Archer, N. Zinc Protamine Insulin. A Clinical Trial of the New Preparation, *Brit. M. J.* **1**: 487-491 (March 6) 1937.

10 Joslin, E. P. Protamine Insulin, *J. A. M. A.* **109**: 497-503 (Aug. 14) 1937.

patients four blood sugar curves were obtained with the insulin administered in one dose at 6 a m, 11 a m, 4 p m and 8 p m, respectively. In 1 case two curves were obtained with the insulin injected at 7 a m and 8 p m. In 2 others the insulin was administered at 7 a m and 11 p m. In each instance one dose of insulin for the twenty-four hours was given. The curves were made only after the patients had been on a specific regimen for more than a week, in order to eliminate the possible effect of the cumulative action of the insulin given under the preceding method of therapy.

REPORT OF CASES

The cases studied are briefly summarized as follows.

CASE 1—E G, a woman aged 42, was admitted to the hospital on May 6, 1934. Pulmonary tuberculosis was first diagnosed in 1924. Diabetes mellitus

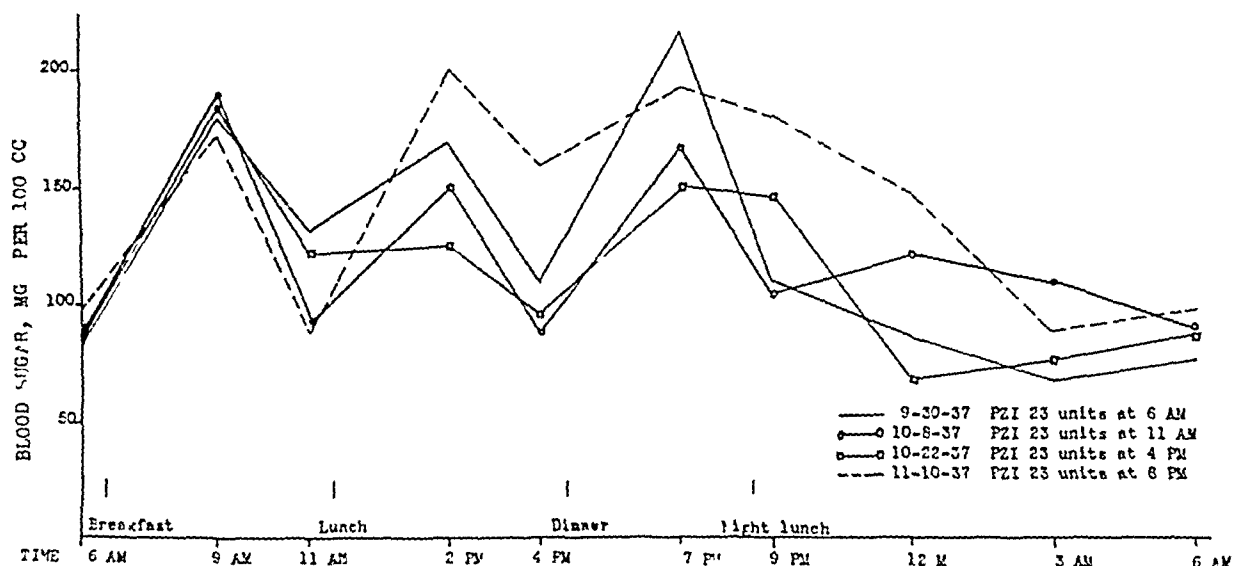


Chart 1 (case 1) —Superimposed blood sugar curves made when protamine zinc insulin was given at 6 a m, 11 a m, 4 p m and 8 p m, respectively. Note the marked similarity of the curves.

was discovered during her stay at the hospital in January 1936. The tuberculosis became arrested after thoracoplasty performed in September 1934. Beginning in November 1936 the diabetes was controlled with a diet of 200 Gm of carbohydrate, 110 Gm of fat and 90 Gm of protein and with 23 units of protamine zinc insulin given at 6 a m. A blood sugar curve was made on Sept 30, 1937. On October 1 the time of administration of insulin was changed to 11 a m, and a second curve was obtained on October 8. The time of the injection of insulin was then changed to 4 p m, and a third curve was obtained on October 22. Beginning on October 23, the insulin was given at 8 p m, and a fourth curve was obtained on November 10. The four curves are superimposed in chart 1. The diabetes was under perfect control throughout the experiment.

Comment—From chart 1 it is evident that, regardless of the time of administration of the insulin, the blood sugar curves in this instance were strikingly similar.

CASE 2—H D, a woman aged 52, was admitted to the hospital on Nov 11, 1936 Diabetes mellitus was discovered in June 1934 Symptoms of pulmonary tuberculosis were noted in November 1935 Pneumothorax was started on the right side in November 1936, and the sputum became free from bacilli in June 1937 Shortly after the patient's admission to the hospital the diabetes was controlled with a diet of 150 Gm of carbohydrate, 110 Gm of fat and 90 Gm of protein and with 30-20-20 units of regular insulin daily Protamine zinc insulin was first used on Jan 27, 1937, and after stabilization the diabetes was perfectly controlled with a single dose of 35 units of protamine zinc insulin given at 7 a m A blood sugar curve was made on March 6 The time of the injection was changed on October 1 to 11 a m, and a second curve was obtained on October 8 Beginning on October 13, the protamine zinc insulin was given at 4 p m, and a third curve

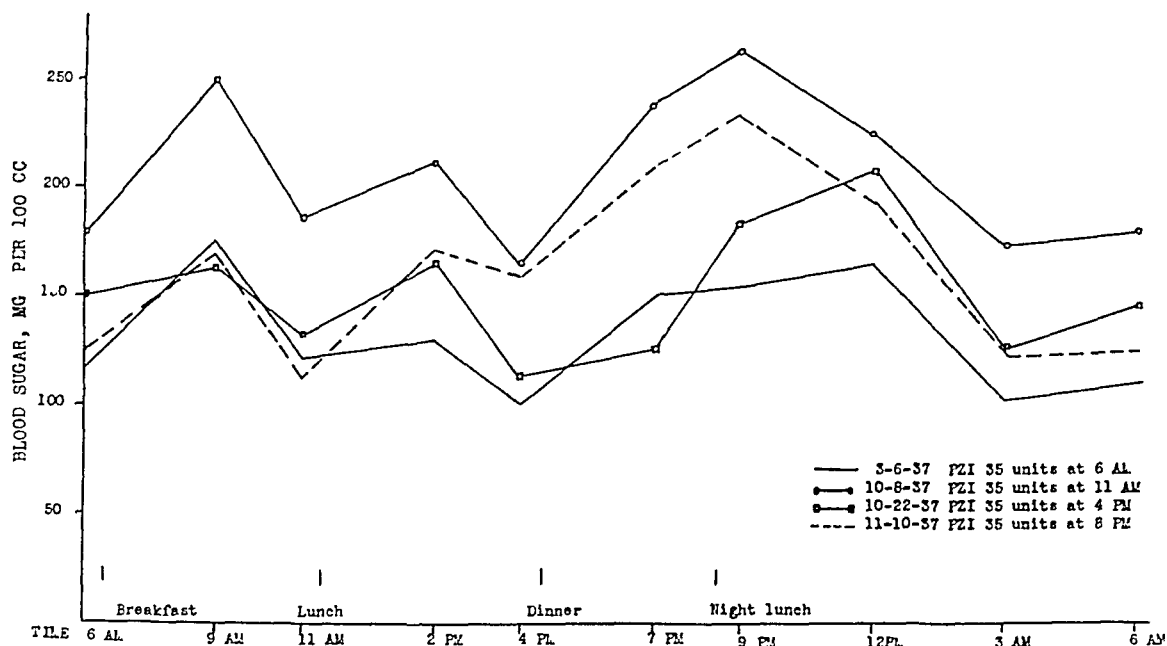


Chart 2 (case 2)—Superimposed blood sugar curves made when protamine zinc insulin was given in one dose at 6 a m, 11 a m, 4 p m and 8 p m, respectively There is a marked similarity in the character of the curves regardless of the time of administration of the insulin Note the elevation of the blood sugar value after each meal and the low value just before meals and during the night

was made on October 22 The time of administration of insulin was changed on October 24 to 8 p m, and a fourth curve was obtained on November 10 The urine was free from sugar throughout the experiment The blood sugar curves are superimposed in chart 2

CASE 3—M M, a woman aged 61, was found to have diabetes in 1932 Pulmonary tuberculosis was discovered in February 1936 The tuberculosis apparently became arrested in September 1936 The diabetes was well controlled

with a diet of 200 Gm of carbohydrate, 110 Gm of fat and 90 Gm of protein and with 40 units of protamine zinc insulin given at 6 a m. A blood sugar curve was obtained on April 16, 1937. A second curve was made on October 8, after the patient had been receiving 30 units of protamine zinc insulin at 11 a m. Because the blood sugar level was elevated, the dose of insulin was raised to 35 units, and beginning on October 12, this was given at 4 p m. On October 22 a third curve was obtained. The time of administration of insulin was then changed to 8 p m, and a fourth curve was made on November 10. The urine remained free from sugar throughout.

Comment—The superimposed curves are shown in chart 3. Although there are minor variations in the character of the curves, the general similarity is apparent.

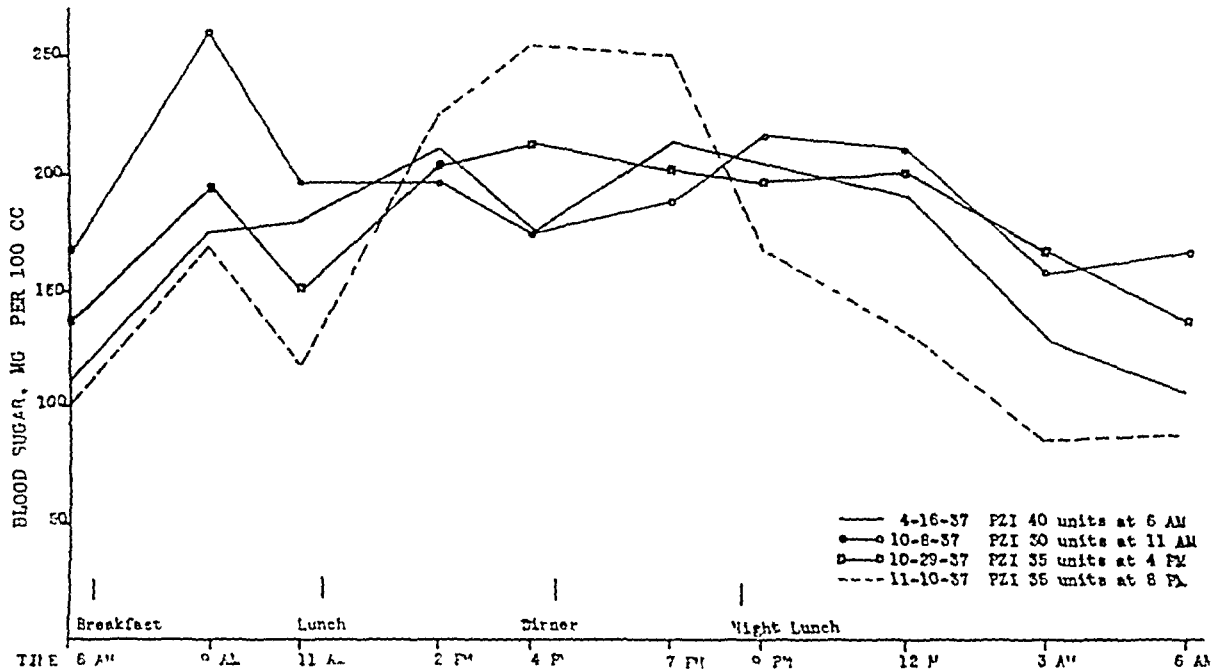


Chart 3 (case 3)—Superimposed blood sugar curves made when protamine zinc insulin was given in one dose at 6 a m, 11 a m, 4 p m and 8 p m, respectively. Note that although there are some variations, there is a general similarity in the character of the curves.

CASE 4—N A, a woman aged 67, was admitted to the hospital on May 29, 1936. Symptoms of diabetes mellitus appeared in 1932, and pulmonary tuberculosis was discovered in January 1936. The patient had been receiving liver extract for pernicious anemia since March 1931. From the time of her admission to the hospital until March 15, 1937, the diabetic condition was controlled with a diet of 150 Gm of carbohydrate, 110 Gm of fat and 90 Gm of protein and with 25-10-15 units of regular insulin. At that time the use of protamine zinc insulin was begun, and she was receiving a single injection of 50 units at 7 a m. In April the dose of insulin was raised to 70 units, and the injection was continued at 7 a m. A blood sugar curve was obtained on December 4. The time of administration was changed to 8 p m on December 6, and a second curve was made on December 22. The two curves are superimposed in chart 4. The urine was free from sugar on the day each of the curves was taken.

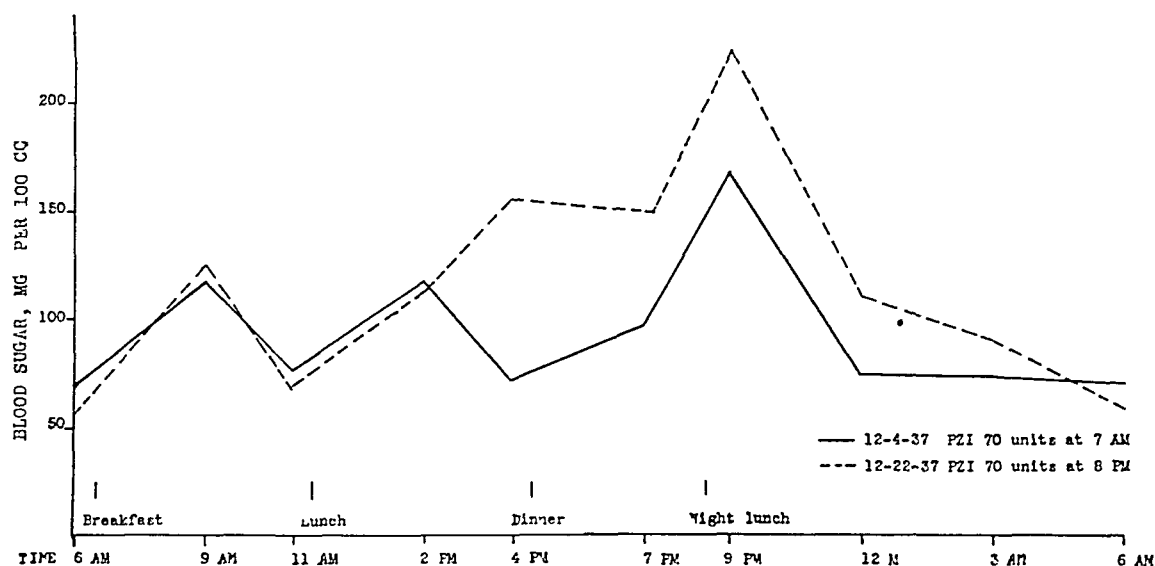


Chart 4 (case 4) —Superimposed blood sugar curves made when protamine zinc insulin was given in one dose at 7 a m and at 8 p m

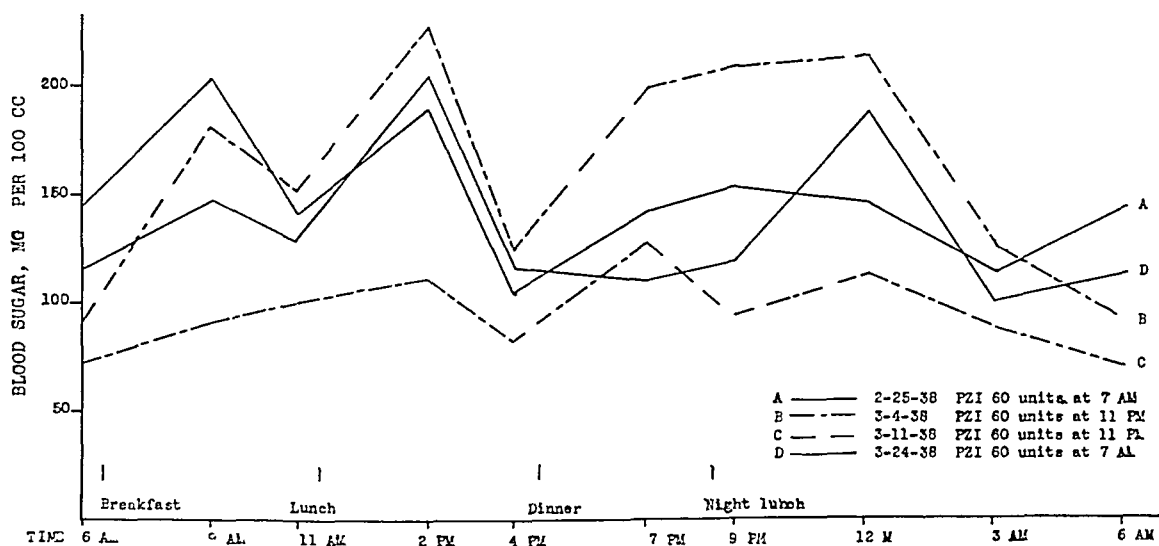


Chart 5 (case 5) —Curves *A* and *D* were obtained when the patient was receiving protamine zinc insulin at 7 a m. Curves *B* and *C* were made when the insulin was given at 11 p m. If only curves *A* and *B* are compared, it appears that there is better utilization of carbohydrate in the morning when the insulin is given at night. However, when curves *C* and *D* are compared, it is evident that there may be considerable variation in the character of the blood sugar curves even though the patient remains on the same plan of therapy.

CASE 5—A M, a man aged 53, was admitted to the hospital on Nov 1, 1937. Diabetes mellitus was discovered in January 1937, at that time symptoms of pulmonary tuberculosis appeared. The patient was receiving a diet of 150 Gm of carbohydrate, 110 Gm of fat and 90 Gm of protein, 60 units of protamine zinc insulin was being given at 7 a m. The first blood sugar curve (chart 5, curve A) was taken on February 25, 1938. The time of injection of insulin was changed on February 26 to 11 p m, and curve B was obtained on March 4. Because there appeared to be a considerable difference in the levels of blood sugar under the two plans of therapy, it was decided to repeat the study. Consequently, the patient continued to receive insulin at 11 p m, and curve C was obtained on March 11. There was considerable difference between this curve and curve B, although the two were taken with the patient under the same regimen. Beginning on March 14, the time of administration of insulin was changed to 7 a m, and curve D was made on March 25. The urine remained free from sugar throughout the experiment.

Comment—A study of the curves in this case reveals the fact that the blood sugar values do not remain constant from day to day even though the patient receives the same diet and the same dose of insulin, given at the same time. If curves A and B are compared, it appears that in the morning the blood sugar value is lower when the insulin is given at 11 p m, but, on the other hand, if curves B and D are compared, little difference is seen in the blood sugar values in the morning. The values were low throughout the day at the time curve C was obtained. It is well to compare this curve with curve B. There is a marked difference between the two, although the patient was on the same plan of therapy at the time these were taken. Obviously, therefore, one cannot arrive at a definite conclusion on the basis of a single observation. It seems reasonable to assume that the variations in the curves are variations that are likely to occur, particularly in severe diabetes, from day to day and are not the result of a change in the time of the injection of insulin.

CASE 6—M F, a man aged 44, was admitted to Sea View Hospital on May 27, 1937. Diabetes mellitus was discovered in 1932. Symptoms of pulmonary tuberculosis appeared in December 1936. The diabetes was at first perfectly controlled with a diet of 150 Gm of carbohydrate, 110 Gm of fat and 90 Gm of protein and with 50-25-30 units of regular insulin. The use of protamine zinc insulin was begun on July 7, 1937, and after stabilization the urine remained free from sugar with the injection of 65 units at 7 a m. On Feb 25, 1938, a blood sugar curve was obtained (chart 6, curve A). On February 26 the time of the injection of insulin was changed from 7 a m to 11 p m, and a second curve was made on March 4. In this case also there appeared to be a marked difference in the blood sugar values, the value in the morning being considerably lower when the insulin was given at 11 p m. Because of this observation it was decided to repeat the determinations. The patient continued to receive the insulin at 11 p m, and a third curve was obtained on March 11. The time of injection was then changed to 7 a m, and a fourth curve was obtained on March 25.

Comment—In this instance, more so than in case 5, there was a marked difference in the blood sugar values in the morning (curves *A* and *B*). If only these two curves had been made, the obvious conclusion would have been that there was much better utilization of dextrose the next morning when the protamine zinc insulin was given at 11 p. m. However, if curves *B* and *D* are compared, there appears to have been better utilization of carbohydrate in the morning when insulin was given at 7 a. m. There was considerable difference in the blood sugar values on the days that curves *B* and *C* were made, although the patient was receiving the insulin at 11 p. m. on both occasions.

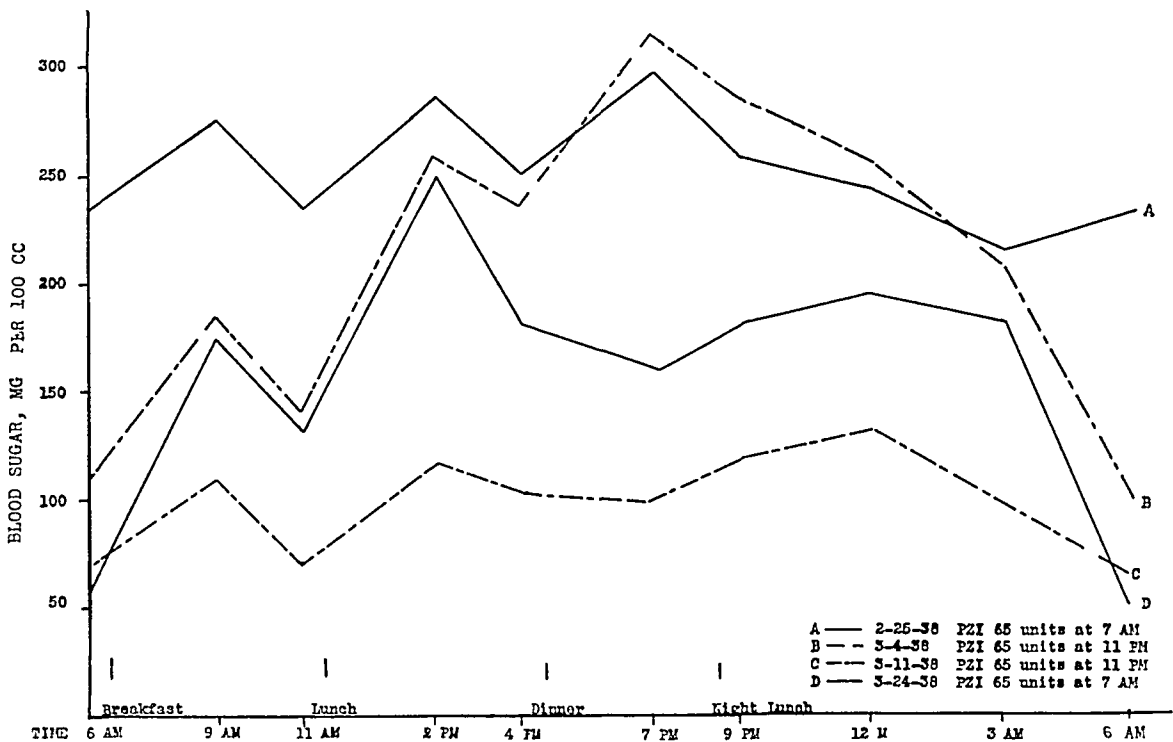


Chart 6 (case 6)—Curves *A* and *D* were made when protamine zinc insulin was administered at 7 a. m. Curves *B* and *C* were made when the insulin was given at 11 p. m. Note the variations in the character of the curves even when the patient was kept on the same regimen.

Similarly, there is a marked difference between curves *A* and *D*, although the insulin in both instances was administered at 7 a. m.

It appears from the findings in cases 5 and 6 that one can expect considerable variations in the blood sugar curves from day to day, independent of the time of administration of the insulin.

COMMENT

Examination of the superimposed blood sugar curves in cases of mild and moderately severe diabetes (cases 1 to 3) reveals the fact that the curves are remarkably similar regardless of the time of admin-

istration of protamine zinc insulin. Minor variations occur, to be sure, but these are no greater than the variations observed when several curves are taken for a patient who remains on the same plan of therapy. The changes can be explained by alterations in intestinal absorption and by changes in the emotional status of the patient.

Obviously, then, it appears, at least in mild and moderately severe diabetes, that the single dose of protamine zinc insulin may be administered at whatever time of day the patient prefers. This, of course, is a definite advantage in the use of the new insulin, since it further relieves the patient of the necessity of living the "time-table sort of existence" that is so essential with the use of regular insulin.

Of the 3 cases of severe diabetes studied, in 1 case (case 4) the blood sugar curves were much alike, and certainly in this instance altering the time of administration of insulin had no effect on the character of the control. In 2 other cases of severe diabetes (cases 5 and 6) it first appeared that there was better utilization of carbohydrate in the morning when insulin was given at night. However, on repetition of the blood sugar studies, the findings suggested that there is considerable variation in the character of the curves from time to time even though the patient remains on the same plan of therapy and that these changes cannot be attributed to alteration in the time of administration of protamine zinc insulin. I am inclined to believe that in cases of severe as well as mild diabetes protamine zinc insulin may be given at any time of day. This opinion is further supported by the fact that in several other cases of severe diabetes, in which blood sugar curves had not been made, altering the time of administration of insulin had no appreciable effect on the glycosuria or the time of appearance of hypoglycemic reactions.

Rabinowitch⁶ has shown that when protamine zinc insulin is given to a patient during fasting, the blood sugar value drops within a few hours to a low point and then remains at a practically constant level for at least thirty-six hours. Examination of the curves in the present study reveals the fact that the lowest values are those obtained just before breakfast, before lunch, before dinner and during the night, that is, during the fasting periods of the day. Furthermore, it is interesting to note that the blood sugar values at these times tend to approach the same level. From this observation, it may be concluded that the probable action of protamine zinc insulin is as follows. It lowers the blood sugar value to a certain level and tends to maintain it at that level for more than thirty-six hours. The larger the dose of protamine zinc insulin, the lower the basic level. The absorption of carbohydrate elevates the blood sugar value, but within a few hours in the cases of mild and moderately severe diabetes the basic level is again reached. Similarly, the basic level is maintained during any period

of fasting. The height to which the blood sugar value will be raised after meals will depend on the amount of carbohydrate taken and the severity of the diabetes. In severe diabetes the postprandial hyperglycemia may be so great that the slowly acting insulin is unable to cope with the situation, and, as a result, the high blood sugar value may be maintained throughout the day, and glycosuria may develop. During the night, however, when there is a prolonged period of fasting, the basic level will be attained.

If the conclusions as to the action of protamine zinc insulin are correct, one should not expect any change in the character of the blood sugar curve resulting from alteration in the time of administration of the insulin. In the patients studied, no appreciable variation was observed that could be attributed to such a change.

SUMMARY AND CONCLUSIONS

A study of the effect on the blood sugar curve resulting from alteration in the time of administration of protamine zinc insulin was made in 6 cases of diabetes.

There was no appreciable effect on the character of the blood sugar curve resulting from a change in the time of injection of protamine zinc insulin.

Variations in the blood sugar levels may occur from day to day even when the patient remains on the same plan of therapy.

The single dose of protamine zinc insulin may be given at the time of day that is most convenient for the patient.

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DELETERIOUS EFFECTS OF EXPERIMENTAL PROTAMINE INSULIN SHOCK

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The effects of hypoglycemia of long duration on the various tissues and on the organism as a whole are of fundamental importance. On the immediate practical side, the possibility of the use of excessive doses of the slowly acting protamine insulin by untrained persons (because of the lack of rapid action) or the accidental administration of the concentrated precipitate from a vial which has not been agitated makes essential a knowledge of the effects of hypoglycemia due to insulin shock. Insulin shock is being purposely used in the treatment of schizophrenia¹ and undesirable effects of this use are also important.

In all of the experiments recorded here protamine zinc insulin of a strength of 40 units per cubic centimeter was used. It was administered subcutaneously. During some experiments² in which hyperalimentation was produced in albino rats by injections of protamine insulin, the first peculiar effects of hypoglycemia of even short duration were noticed. When the food box became empty or the dose of insulin was so large that the animals were unable to eat sufficient food to prevent the occurrence of hypoglycemia, insulin shock ensued, with the characteristic convulsions and coma. Determinations of the dextrose content of blood from the tail or from the heart by a method³ which gives approximately true values for dextrose were found to range from 0 to 27 mg. per hundred cubic centimeters, depending on how near a convulsion (which would tend to raise the value) the specimen had been taken. No amount of dextrose in an appropriate concentration given by stomach tube or intraperitoneally would rescue these rats. The concentration of sugar in the blood was often checked, and even when it was raised to above 100 mg. per hundred centimeters and kept above this level the rats

From the Scripps Metabolic Clinic

A preliminary report of some of the experiments described in this paper has been published (*Proc. Soc. Exper. Biol. & Med.* **36**: 515, 1937).

1 Sakel, M. *Neue Behandlung der Schizophrenia*, Vienna, M. Perles, 1935.

2 MacKay, E. M., and Callaway, J. W. Hyperalimentation in Normal Animals Produced by Protamine Insulin, *Proc. Soc. Exper. Biol. & Med.* **36**: 406, 1937.

3 Somogyi, M. A Method for the Preparation of Blood Filtrates for the Determination of Sugar, *J. Biol. Chem.* **86**: 655, 1930.

always died from ten minutes to four hours later. A total of 38 animals in such accidental or planned experiments were followed. The occasional death which occurred soon after sugar was administered will be considered in connection with the similar behavior of dogs. Almost all of the other rats died, apparently from respiratory failures, with hypoglycemia or with the sugar content of the blood raised to normal but without any effect on the symptoms. A variable degree of hemorrhagic edema of the lungs was always observed. Some time before death the pulmonary pathologic condition was evidenced by the oozing of blood-tinged serous fluid from the nostrils of the comatose rat. This recalled the behavior of rats which we had once observed after an overdose of epinephrine, and the possibility occurred to us that the effect of insulin was, at least in part, an overproduction of epinephrine during the hypoglycemia. Although we have been able to demonstrate high concentrations of epinephrine in the blood of the rats with insulin shock we have been unable regularly to prevent the development of the pulmonary pathologic condition in insulin-treated rats by prior removal of the adrenal medullas with sufficient time allowed for regeneration of the cortical tissue. Further study of this pulmonary edema, which occurs as a result of prolonged hypoglycemia in the albino rat but not in dogs, is warranted. Histologically it is similar to the neuropathic pulmonary edema which occurs when both vagus nerves are cut in the rabbit or in the guinea pig⁴. This occurs regularly when the vagi are severed in the rat, but it is interesting in view of the effects of insulin that in our hands, at least, such a procedure causes no serious symptoms in the dog. However, Prof. Maurice B. Visscher wrote us that Dr. Victor Loibel, working in his department, has found that the pulmonary edema caused by vagotomy is not truly neuropathic. He has found that if one vagus nerve is cut below the recurrent laryngeal nerve and the other above it, the rat or guinea pig does not die. He concluded that the edema which follows bilateral cervical vagotomy is the same type as that which occurs in any type of tracheal obstruction.

When dogs were given protamine insulin in sufficient doses to maintain hypoglycemia for periods of thirty hours or more, often with no convulsions but only a condition of deep stupor, the administration of dextrose by stomach tube during this period gave rise to fatal convulsions. Bollman⁵ has made similar observations. Six of our animals died in this manner. It also happened occasionally with the hypoglycemic rats. A typical protocol follows.

4 Farber, S. Studies on Pulmonary Edema. I. The Consequences of Bilateral Cervical Vagotomy in the Rabbit, *J. Exper. Med.* **66** 397, 1937, Studies on Pulmonary Edema. II. The Pathogenesis of Neuropathic Pulmonary Edema, *ibid.* **66** 405, 1937.

5 Bollman, J. L., cited by Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **59** 341 (Feb.) 1937.

EXPERIMENT 1—A mongrel bitch weighing 29 Kg was kept without food for twenty-four hours, at the end of which period the value for blood sugar was 57 mg per hundred cubic centimeters. Sixty units of protamine zinc insulin was given. At the end of one and one-half hours the value for sugar in the blood was 55 mg. At the end of ten hours the dog was nervous. After nineteen hours the value for blood sugar was 22 mg. Fifty units of insulin was given. At twenty-two hours the value for blood sugar was 23 mg and the dog was comatose. At twenty-seven hours the value for blood sugar was 18 mg, and the animal made an occasional movement. At thirty-two hours the value for blood sugar was 6 mg. At forty-three hours the animal had a convulsion. At fifty hours the value for blood sugar was 22 mg, and the dog was in deep coma. At fifty-five hours the value for blood sugar was 15 mg. At sixty-one hours 200 cc of a 25 per cent solution of dextrose was given by stomach tube. At sixty-one and one-quarter hours there was a convulsion. At sixty-one and one-half hours the value for blood sugar was 54 mg and convulsions were almost continuous. At sixty-one and seven-tenths hours the animal died.

The convulsions and sudden death were similar to the results of administrations of water⁶ to previously dehydrated rabbits. After a number of trials we were able to produce convulsions and sudden death in 1 comatose hypoglycemic dog by giving water alone. Four of 9 rats in which the experiment was tried were killed in this way. Bollman⁷ found that dogs which died in such attacks showed multiple petechial hemorrhages scattered throughout the brain. We observed such hemorrhages in the brain of only 1 dog, and this animal did not die suddenly when dextrose was first given but lingered for nearly twenty hours. The causes of sudden death when dextrose is given in cases of hypoglycemia are probably sudden electrolyte shift and hemoconcentration superimposed on cerebral stasis and degenerative changes which have been produced in the nerve tissue.⁷ Allen and Vicens⁸ have recently pointed out that the effects of shock and of large doses of insulin are mutually aggravating. It is possible that when the organism dies from insulin poisoning, even after the sugar content of the blood has been restored to normal and without improvement in the general condition, the condition of circulatory shock which contributes to death from excessive doses of insulin, apart from the blood sugar level per se, is so serious that ultimately it would cause death under any circumstances. Death would be hastened in these conditions by the administration of strong solutions of dextrose or by any other therapy which would tend to alter the concentration of the body fluids too rapidly.

6 MacKay, L. L., and MacKay, E. M. Convulsions Resulting from Fluid Administration Following Sucrose Injections and Water Abstinence, *Proc Soc Exper Biol & Med* **21** 286, 1924.

7 Riggs, H. E., and Griffiths, J. O. Pathologic Changes in the Nervous System Incident to Alterations in the Physiologic Dynamic Equilibrium of the Blood (Insulin Shock), *Arch Neurol & Psychiat* **39** 643 (March) 1938.

8 Allen, F. M., and Vicens, C. A. Surgical Treatment of Experimental Insulin Poisoning, *Endocrinology* **24** 230, 1939.

The most interesting of the deleterious effects of poisoning with protamine insulin are the evidences of permanent damage to the brain. This is hardly surprising in view of the importance of an adequate supply of carbohydrate for the metabolism of the brain cells. Marked hypoglycemia is known to depress the metabolism of the brain,⁹ and degenerative changes have been observed in the ganglion cells of the brains of patients and animals given large amounts of insulin.¹⁰ Both sensory and motor disturbances ensued as a result of long-continued hypoglycemia. We shall consider here only those animals in which the concentration of blood sugar had returned to normal for at least four days. Impairment of vision and hearing as well as complete blindness and deafness developed. In 2 instances there resulted incessant restlessness and a complete disorganization of the emotional complex. Motor disturbances were the most common, incoordination, spasticity and even paralysis resulting from the long lowered sugar content of the blood, with consequent reduction in the metabolism of the brain. Details of only 1 experiment are given in the typical protocols which follow.

EXPERIMENT 2—A mongrel bitch weighing 20.1 Kg. was kept without food for two days and was then given 40 units of insulin. The value for blood sugar was 62 mg. per hundred cubic centimeters. At three hours this value was 51 mg., and at eight hours it was 33 mg. At eleven hours 20 units of insulin was given. At twenty-two hours the value for blood sugar was 20 mg. Twenty units of insulin was given. At twenty-six hours the value for blood sugar was 15 mg. Ten units of insulin was given. At twenty-eight hours there was a severe convulsion followed by coma. At thirty-eight hours the animal was still comatose, with an occasional convulsion. At forty-four hours the value for blood sugar was 8 mg., 50 gm. of dextrose in 20 per cent solution was given by stomach tube. At fifty-four hours the animal was recovering slightly and was given 30 units of insulin. At fifty-eight hours the value for blood sugar was 0. There were numerous convulsions. At seventy hours the animal was still in coma, with occasional convulsions. At seventy-eight hours 10 units of insulin was given. There was no change in the animal's condition. At ninety hours 20 units of insulin and, in addition, 200 cc. of 1 per cent sodium chloride by stomach tube were given. At ninety-four hours the value for blood sugar was 6 mg. Two hundred cubic centimeters of saline solution was given. At one hundred

9 Dameshek, W., and Myerson, A. Insulin Hypoglycemia. The Mechanism of Neurologic Symptoms, *Arch Neurol & Psychiat* **33** 1 (Jan) 1935. Himwich, H. E., Bowman, R. M., Wortis, J., and Fazekas, J. F. Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, *Science* **86** 271, 1937.

10 Wohlwill, F. Ueber Hirnbefunde bei Insulin-Ueberdosierung, *Klin Wchnschr* **7** 344, 1928. Terplan, K. Changes in the Brain in a Case of Fatal Insulin Shock, *Arch Path* **14** 131 (July) 1932. Bodechtel, G. Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, zugleich ein Beitrag zu seiner Pathogenese, *Deutsches Arch f klin Med* **175** 188, 1933. Weil, A., Liebert, E., and Heilbrunn, G. Histopathologic Changes in the Brain in Experimental Hyperinsulinism, *Arch Neurol & Psychiat* **39** 467 (March) 1938. Moersch, F. P., and Kernohan, J. W. Hypoglycemia. Neurologic and Neuropathologic Studies, *ibid* **39** 242 (Feb) 1938.

and two hours the animal was still in coma. Three hundred cubic centimeters of milk was given. At one hundred and ten hours the temperature was 36 C (96.4), 50 Gm of dextrose in 300 cc of milk was given. At one hundred and twelve hours there were practically no convulsions, but the animal was still comatose. At one hundred and twenty-four hours the animal was commencing to regain consciousness. It was still being forcibly fed. At one hundred and thirty-six hours it attempted to stand. With careful feeding and the warmth of a hot pad the animal gradually recovered from the insulin coma. There was marked spasticity of the posterior extremities, and this persisted as a permanent result. It was finally discovered that the dog was totally blind, and there was no evidence of function of the olfactory nerve. Food placed in the mouth was swallowed and if the nose was rubbed in it it would be taken and swallowed. Non-edible material, however, was taken just as readily. During the ensuing three weeks there was no improvement in this animal's condition.

EXPERIMENT 3—A male collie weighing 32 Kg was given a total of 125 units of insulin over a four day period. The dog was in coma, with a variable number of convulsions, for forty-two hours of the first three days. All of the fourth and fifth days were spent in coma, with only an occasional convulsion. Administration of dextrose was commenced, and in three days the animal reached the maximum recovery. Residual damage to the brain resulted in impaired hearing but not in total deafness. The dog had formerly been quiet and now was restless, moving about his cage incessantly. Before the insulin shock he had been docile and had liked attention. Now snarling greeted any one's approach and he could be handled only with difficulty.

EXPERIMENT 4—A male German shepherd dog weighing 41 Kg was kept in insulin coma with the usual incidence of convulsions, for eighty-eight hours in five days by the use of 145 units of insulin. When it recovered it was entirely normal except for hemiplegia on the right. This persisted and showed no tendency to clear up during the following weeks.

EXPERIMENT 5—A mongrel terrier bitch weighing 10.5 Kg was kept in coma for almost all of three days by the use of 75 units of insulin. Convulsions were extremely numerous. After recovery there was noticeable spasticity of the posterior extremities, a peculiar twitching of the head, failure to wag the tail or show the usual friendliness when called by name and loss of most of the sight in the left eye.

All of the animals used in these experiments were killed after they had been observed for three weeks after the cessation of hypoglycemia. There was no evidence of suffering, but it seemed unwise to continue life longer for the pathologic condition of the brain was indirectly the source of some discomfort.

Apart from the fatal effects of overdoses of protamine insulin, which Allen and Vicens⁸ have emphasized, recovery with permanent cerebral pathologic conditions represents an important undesirable effect not only of accidental overdosage but of treatment of neural disease with this drug. Gellhorn¹¹ has pointed out not only that the nervous system

11 Gellhorn, E. Effects of Hypoglycemia and Anoxia on the Central Nervous System. A Basis for a Rational Therapy of Schizophrenia, *Arch Neurol & Psychiat* 40 125 (July) 1938.

is influenced by hypoglycemia in a manner similar to that in which it is affected by anoxia but that hypoglycemia sensitizes the central nervous system to anoxia so far as functional effects are concerned¹² If this is so, it should also be true of pathologic changes, and it probably is, the case of the hypoglycemic condition is doubly important, for the condition of the circulation in insulin shock is frequently contributory to a state of anoxia. It is possible that administration of oxygen as well as injections of dextrose would be desirable in cases of serious overdosage with insulin. We plan to examine this point experimentally.

SUMMARY

Overdosage with protamine zinc insulin produced the characteristic coma and convulsions in the rat. If the duration of the insulin shock was not short, the administration of dextrose in amounts sufficient to raise the blood sugar level to a normal value was without influence. Death from respiratory failure always ensued, and there was usually marked edema of the lungs.

The administration of strong solutions of dextrose by stomach tube to rats or dogs or intraperitoneally to rats which have been in insulin shock for some time is frequently followed by convulsions and sudden death. Administration of water occasionally has the same effect. These results are probably due to a sudden electrolyte shift and changes in the concentration of the body fluids superimposed on an impaired general circulation and cerebral stasis and to degenerative changes consequent on the preceding hypoglycemia.

Hypoglycemia is known to affect the metabolism of the brain in an adverse manner and to give rise to degenerative changes. We found evidence that prolonged hypoglycemia led to permanent functional damage to the brain. After long periods of hypoglycemia due to the administration of protamine zinc insulin over a period of three to five days, permanent sensory and motor disturbances ensued. The dogs had impairment or complete lack of vision or hearing, disturbances of the emotional complex, incoordination, spasticity and even paralyses.

These results show once more the necessity for great care in preventing unnecessary hypoglycemia. The administration of insulin should be carefully controlled. The shock should be maintained for as short a time as possible when it is produced for therapeutic purposes.

12 Gellhorn, E., Ingraham, R. C., and Moldavsky, L. The Influence of Hypoglycemia on the Sensitivity of the Central Nervous System to Oxygen Want, *J. Neurophysiol.* **1**, 301, 1938.

Eli Lilly and Company supplied the protamine zinc insulin used in the early part of this study. Additional supplies were furnished by E. R. Squibb & Sons.

TRANSPORT OF AIR ALONG SHEATHS OF PULMONIC BLOOD VESSELS FROM ALVEOLI TO MEDIASTINUM

CLINICAL IMPLICATIONS

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EXPERIMENTAL INVESTIGATIONS

Pulmonic Interstitial Emphysema—That air, after it has broken from the pulmonic alveoli into the interstitial tissue of the lung, can travel along the sheaths of the pulmonary blood vessels, in artificial channels which it dissects for itself, to the root of the lung, and from there into the mediastinum, has been amply demonstrated in a series of experiments on cats and other animals¹ The alveoli are made to leak by overinflating them, and so stretching and straining the walls This is accomplished by passing a truncated catheter into a region of the lung (the lower lobe of the right lung is conveniently used) and blowing air into it, thus extending the alveolar walls and producing many small ruptures in their floors, which overlie the small branches of the pulmonary blood vessels It is important to visualize clearly this locus of the leakage,² the area of which varies in size depending on the volume of lung thus hyperinflated Continuance of the blast means persistence of the air leakage and onward movement of the air through these artificial tunnels in the vascular sheath, which increase in size as they are followed toward the root of the lung

Air bubbles in the pulmonic arterial and venous sheaths may easily be seen with the naked eye at the roots of the lungs in the freshly opened thorax By careful inspection and probing the situation of the air in the vascular sheaths can be demonstrated By slicing the fresh lung the bubbles can be seen, but with greater difficulty, and then only in the region of the hilus in the animal lungs It is not easy to determine their exact relation to the blood vessels under these conditions, for the

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1 Pulmonic perivascular emphysema so induced has been studied intensively in material from 12 cats In addition, 23 other animals (14 cats and 9 rabbits) have been experimented on to clear up special points

2 Macklin, C C Pneumothorax with Massive Collapse from Experimental Local Over-Inflation of the Lung Substance, *Canad M A J* **36** 414, 1937

air diffuses out quickly, and the operation of slicing, even when carefully done with a sharp knife, disturbs its relations, and even leads to its evacuation. Thus it is necessary to rely on properly fixed material.

We have found that fixation is best accomplished by removing the collapsed lungs from the animal immediately after the experiment and filling them by way of the bronchial tree with a fixative (40 per cent solution of formaldehyde diluted 1:10, Zenker's fluid and others were used). The lungs were then immersed in the same fluid and allowed to stand for a day or two, until well hardened. Thin sections were cut from various parts, extending from the region of overdistention to the root of the lung. Blocks 2 mm or more in thickness were cut transversely or longitudinally to the long axis of the pulmonary blood vessels and examined with the binocular microscope, these were very instructive, for in a series of such pieces it was possible to trace the track of the air from the sheaths of the finer vessels, which had been invaded, down the vascular tree to the large sheaths of the pulmonic vascular stems at the roots. In these fixed tissues the air has, of course, diffused out but the pattern of the bubbles remains. It often is found that the vessel is obviously encroached on by the bubbles, and may even be completely collapsed by the pneumatic armature. In figure 1 the arterial and venous branches seen are each separated from the enviroing lung tissue by a thick zone of air. The former loose, succulent connective tissue of the sheath has been greatly distended, indeed little or nothing is seen of this original tissue but thin strands joining the lung substance with the wall of the vessel. The blood flow in such a part must be almost, if not completely, stopped. In figure 2 the invasion of air is of more moderate degree, but even here it is plain that the air would impose a circulatory handicap. The most striking accumulations are in the roots of the lungs where the converged air streams have merged into large blebs. Here the air block is of strategically greater importance than it is more peripherally, for it impinges on main trunks rather than on smaller branches. The end result would obviously be a serious impediment to the pulmonary circulation. In experimental animals I have never observed the air in the sheaths of the bronchi nor in those of the bronchial blood vessels. Thus pulmonic interstitial emphysema is primarily an affair of the sheaths of the pulmonic blood vessels. There are, particularly in the region of the hilus in larger lungs, extensions of air into contiguous connective tissue formations, but in this experimental material pulmonic interstitial emphysema was practically synonymous with pulmonic perivascular emphysema.

Pneumomediastinum—Further leakage into the peripheral interstitium of the lung may cause the three dimensional air mass to break through into the mediastinum, and so the tissues here are distended with large blebs. The pressure may become so great that escapes must be

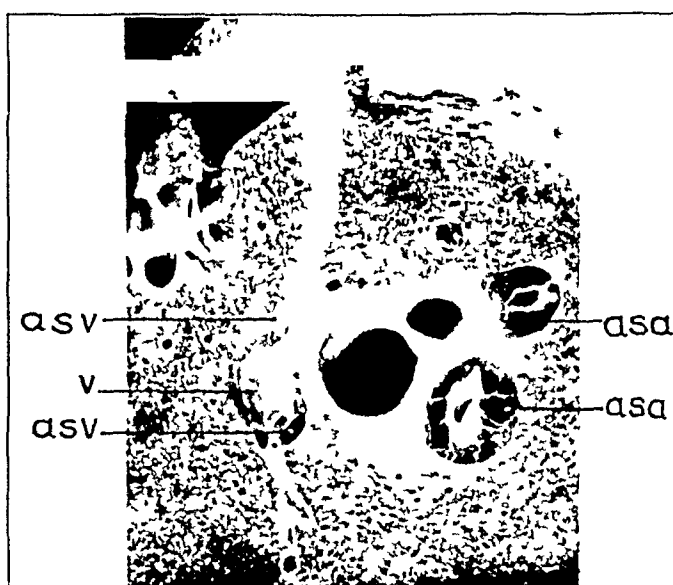


Fig 1—Photomicrograph ($\times 28$) of a thick transverse, freehand slice through the region of the hilus of the lower lobe of the right lung of a cat which had been subjected, while alive and under anesthesia induced with ether and dial (2 cc injected intraperitoneally), to hyperinflation with pure air blown in through a catheter inserted by way of an opening in the trachea, just below the larynx. The pressure was 2 cm of mercury at the beginning and was increased 2 cm each minute for a total of six minutes of continuous insufflation until a maximum of 12 cm of mercury was attained. The insufflation was pressed until the animal's chest and abdomen were well distended.

The bronchus has been cut at a fork. The main stem of the bronchus is the large rounded, dark spot near the center of the field; its branch is the smaller rounded spot to the right and above. No air is seen in the bronchial sheaths. Two branches of the pulmonary artery are seen—one to the right of the main bronchus and one to the right of the branch. Each is entirely surrounded by an air space, *asa*. The cobweb-like formation of connective tissue, representing the strands that remain to connect the wall of the artery with the outer boundary of the vascular sheath, is well seen around the larger arterial branch. The pulmonary vein (*v*) is seen to the left of the main bronchus. It has been cut obliquely and is not as plainly shown as are the arteries. Around it is the air space *asv*.

This is a good example of a case of marked pulmonary vascular interstitial emphysema induced experimentally by prolonged local overinflation of a region of the lung, as seen around the larger blood vessels of the hilus, under low power. There was double pneumothorax in this case, with complete massive collapse. Immediately after the massive collapse occurred, the lungs were carefully removed and filled with Bouin's fluid, by means of a cannula in the trachea, to the degree of normal inflation. They were sectioned after hardening in this fluid.

The lumens of arteries and veins have been almost obliterated by the pressure of the air in the sheaths, so that the blood flow must have been almost completely stopped. Air in the mediastinum and retroperitoneum added to the circulatory impediment.

found, I have met air freshets breaking through downward—into the retroperitoneal space (with even further onflow into the groin and leg), upward into the root of the neck, face, axilla, wall of the chest and arm, forward between the parietal pleura and the pericardium, to appear as blebs overlying the heart (pneumoprecordium), and laterally into the opposite lung or unbloated parts of the same lung. Of course, the air in the mediastinum and contiguous regions interferes further with the function of the vascular system. The heart and great vessels are pressed on, it may be grievously. Ballou and Francis³ induced a fall in blood pressure in animals by increasing the intramediastinal pressure. The coronary vessels must be compressed in marked cases, and it seems likely that the current within them is slowed. Embarrassment occurs similarly in all other blood vessels which are implicated in the spread of the emphysema, but it must be in minor degree where the region is unconfined and the environing pressure not greatly raised. The most important blockade is in the mediastinum and lung. In my experimental animals there was, in extreme cases, such obstruction that the circulation was stopped. As an incident in the course of experimental pneumomediastinum we observed pneumothorax, and in the cases investigated it was caused by rupture of the mediastinal wall, strained past endurance.² Its effect is to relieve the pressure in the mediastinum and lung, thus freeing the circulation, at the same time, by collapsing the lung, it stops the further leaking of air into the vascular sheaths. Unfortunately, in these animals it was always double and complete, and hence was incompatible with continuance of life.

CLINICAL PARALLELS

There are clinical parallels for this condition of pulmonogenic pneumatization of the interstitial tissues, and for all aspects of it, particularly pulmonary interstitial emphysema and pneumomediastinum. Contributions to the literature have recently been numerous.

Pulmonic Interstitial Emphysema—This condition in man, as in animals, is fundamentally emphysema of the vascular sheaths. True, there are often extensions from these sheaths into the adjoining connective tissue, and the air sometimes dissects along a trabecula of connective tissue to the pleura, to form a bleb under it, particularly in the region of the root. It is possible that these blebs rupture at times, to cause pneumothorax, as some authors have stated. I have seen an excellent example of air canalization of the sheaths of the pulmonic vessels in a human lung which had been properly fixed. The reason

3 Ballou, H. C., and Francis, B. F. Consequences of Variations in Mediastinal Pressure. Mediastinal and Subcutaneous Emphysema, *Arch Surg* **19** 1627 (Dec., pt. 2) 1929.

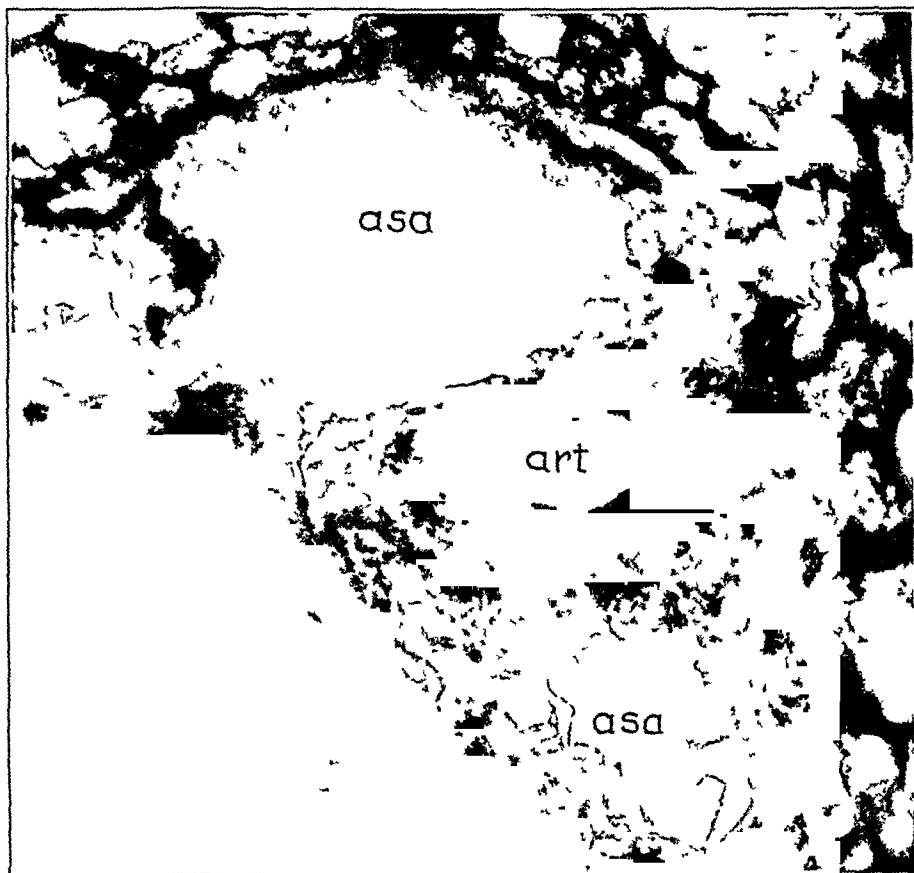


Fig 2—Photomicrograph of a thick frozen section, stained with the Mallory technic. Magnification, $\times 86$. This tissue was from the lower lobe of the right lung of a full-grown cat which had been subjected, while alive and under anesthesia induced with ether, to insufflation of air charged with osmic acid vapor, introduced via a catheter, for a period of twelve minutes. The catheter tip was observed at autopsy in the main bronchus of the lower lobe of the right lung. There were double pneumothorax and massive collapse. The lungs were removed one-half hour after death and filled, by way of the trachea, with Orth's fluid to the extent of ordinary inflation. Frozen sections were cut after the material was hardened. The osmic acid vapor had nothing primarily to do with the perivascular interstitial emphysema.

Near the center of the field is seen a contracted branch of the pulmonary artery, *art*. Above and below it are artificial air spaces, *asa*. In the fresh condition the presence of air bubbles makes these spaces smooth in contour, but the air has been replaced by the reagents used and the walls of the spaces appear ragged. Part of a bronchial wall is seen in the lower left corner. The average diameter of this branch of the pulmonary artery, in the fixed and dehydrated condition, is about 0.3 mm. This is a good example of invasion of air and canalization of the sheaths of the smaller branches of the pulmonary artery. The presence of the air diminishes the caliber of the blood vessel and impedes the circulation.

that so little has been known about the exact location of air in the interstitium of the human lung is because (1) fixation has been delayed until much, or indeed all, of the air has diffused out, and (2) fixation has been by immersion of the excised contracted pieces, from which the air has escaped. Further research by better methods is needed on the histopathologic changes induced by aberrant air in the human pulmonic interstitium. Fixation should be immediately after death, and by injection into the bronchial tree.

Cases of pure pulmonic interstitial emphysema have not been well differentiated clinically. Roentgenographic demonstration is not easy. The condition is often so complicated by pneumomediastinum and its sequelae that it is difficult to isolate cases symptomatically. Even when the air has not diffused beyond the lung there is undoubtedly an impediment to the circulation, and the degree of this would depend on several factors, among them the extent of the area of leakage. The fact, however, that in the lungs the largest air blebs gather at the root, where they compress the greater vessels and can do most damage, makes a small area of leakage assume an importance out of all proportion to its size. The sheaths are apparently able to stretch to a considerable degree, to make room for the invading air, but when they are well pneumatized as I have seen them, the vessels are collapsed and appear to be clamped, as it were, in an air vise.

Does this pressure and interference with the flow elicit pain, particularly from the obstructed arteries? This question has been raised,⁴ but as yet there is no answer. Certainly there are many cases in which pain in the lateral portion of the chest ushers in the outspoken signs and symptoms of pneumomediastinum. Hamman,⁵ Moiey and Sosman,⁶ Phillips,⁷ Maxwell⁸ and many others mentioned lateral pain. Sometimes it is sharp, sometimes it is described as a "stitch" in the side. Between the time of onset of the lateral pain and that of the precordial pain of pneumomediastinum there is often an interval such as would presumably allow for the transit of the air from the vascular sheaths into the mediastinum.

Thus, the most important point about pulmonic interstitial emphysema seems to be the associated circulatory embarrassment. It must

4 Macklin, C. C. Spontaneous Mediastinal Emphysema. A Review and Comment, *M. Rec.* **150** 5, 1939.

5 Hamman, L. Spontaneous Mediastinal Emphysema, *Bull. Johns Hopkins Hosp.* **64** 1, 1939.

6 Morev, J. B., and Sosman, M. C. Spontaneous Mediastinal Emphysema, *Radiology* **32** 19, 1939.

7 Phillips, P. Subcutaneous Emphysema During Labour, *Brit. M. J.* **1** 54, 1938.

8 Maxwell, J. Spontaneous Haemopneumothorax, *Brit. M. J.* **1** 778, 1938.

not be forgotten, too, that infections may travel from the alveoli along these "false" channels, so starting inflammatory foci on the course of the blood vessels and in the mediastinum. Imperatori⁹ mentioned such a case.

Pneumomediastinum.—Although pneumomediastinum has been recognized clinically for a long time, there has been a recent revival of interest in it, and some important points have been emphasized. One of these is the curious crunching sound which is heard over the region of the heart in some cases and which, on account of the prominence given to it by Hamman,⁵ may be known as Hamman's sign. This noise was attributed by Hamman, and I think with good reason, to the presence of air between the anterior parietal pericardium and the thoracic cage. I have noted frequently in my experimental animals that, on removal of the sternum and costal cartilages, a froth of bubbles of different sizes overlying the parietal pericardium, was conspicuous. These bubbles had evidently worked themselves forward from the posterior part of the mediastinum. Agitation of them by the heart's action gives rise to the characteristic sound, which Hamman stated may sometimes be heard with the unaided ear. I have never observed air bubbles within the pericardial cavity in animals. No doubt there are many cases in which the air does not extend forward around the heart, and then there would be pneumomediastinum without the crunching sound. In these cases Hamman said that the roentgenographic evidence of air in the mediastinum may be decisive. Thus the absence of Hamman's sign does not rule out emphysema of the mediastinum. In the usual posteroanterior or anteroposterior projections it is only the more outlying pockets of air that can be seen. Lateral and oblique¹⁰ projections should also be used. There are certainly many degrees of invasion of air, from a few small bubbles in the posterior portion of the mediastinum to the extreme inflations with eruptions into contiguous territory, as already described, and with rupture of the wall into the pleural cavity.

The pain of pneumomediastinum has often been emphasized. It seems to depend largely on the amount of distention, and has been described as sharp and stabbing.⁵ It is in the precordial area. In cases in which the initial pain is lateral I suspect that it originates in the pulmonic interstitial tissue or pleura rather than in the mediastinum. The nature of the pain and its line of irradiation, sometimes down the left

9 Imperatori, C. J. Pericarditis as a Terminal Lesion in Mediastinitis. Report of a Case Following Inhalation of a Foreign Body in the Bronchus and Accompanied by Spontaneous Emphysema, *Ann Otol, Rhin & Laryng* **42** 923, 1933.

10 Andrus, P. M. A New Method for the Radiographic Exploration of the Mediastinum and Concealed Portions of the Pulmonic Fields, *Radiology* **23** 97, 1934.

arm, have led to the erroneous diagnosis of coronary occlusion. It is possible that the thrust of the air even through both layers of pericardium may indent the coronary blood vessels and so cause anginoid pain. The peculiar crunching noise has doubtless been taken for a pericardial rub. Thus, on account of mediastinal emphysema, unfavorable prognoses have been made baselessly.¹¹

It is remarkable how speedily the air is absorbed from the mediastinum when its inlet is stopped and proper therapeutic measures are taken. One to two weeks, with appropriate treatment, is usually sufficient for its disappearance. Noteworthy, too, is the extent of the spread of air that may occur without entailing a really critical condition. The neck, face, chest and other parts of the patient may look severely bloated, yet he may soon regain his normal appearance. Sometimes, however, the area of pulmonic leakage is extensive, with copious infiltration of the vascular sheaths, as, for instance, in cases of bronchial impaction by foreign bodies in which a main stem is occluded, leading to serious diminution in lung volume through absorption of the air. Here the compensatory alveolar ectasia may be voluminous and of a severe type. The leaking area may be on the same side as the atelectasis, or it may be in the opposite lung, or in both. When the interstitial air pressure in the lungs and mediastinum embarrasses the circulation markedly there are dyspnea, cyanosis and dilatation of the right side of the heart. Pneumothorax, intervening by rupture of the mediastinal wall, as in my experimental animals, and possibly also in man, or by rupture of a subpleural bleb in the region of the root, connected, as already described, with the air-inflated vascular sheaths, relieves the impediment to the circulation and stops the leak by overcoming its cause, the hyperinflation. It may thus be regarded as a natural therapeutic method. It is often slight in degree,⁵ and does not always occur spontaneously in these cases. If the patient is in a critical condition it may be necessary to remove the air. The root of the neck may be incised and the air drawn off with a suction apparatus (Tiegel¹²). A hard rubber catheter may be inserted from the root of the neck into the mediastinum, or the surgical method of Furstenberg and Yglesias¹³ may be used. Artificial pneumothorax on the side of the leak is likely to put an end to further transport of air and invasion of the mediastinum by correcting the overinflation which lies at the basis of the leaking

11 Hamman, L. Spontaneous Interstitial Emphysema of the Lungs, *Tr. A. Am. Physicians* **52** 311, 1937.

12 Tiegel, M. Ein einfaches Verfahren zur Bekämpfung des mediastinalen Emphysems, *Zentralbl. f. Chir.* **38** 420, 1911.

13 Furstenberg, A. C., and Yglesias, L. Mediastinitis. A Clinical Study with Practical Anatomic Consideration of the Neck and Mediastinum, *Arch. Otolaryng.* **25** 539 (May) 1937.

Mode of Air Leakage—A few further details as to the mechanics of leakage of air from the alveoli may here be in order. The aberrant air, as has been seen, enters the vascular sheaths through numerous minute openings in the floors of the alveoli which overlie the finer ramifications of the pulmonary arteries and veins. These ruptures, which are situated in the meshes of the capillaries, are brought about by (a) undue stretching and weakening of these alveolar bases during overdistention of the part with air, and (b) a pressure gradient from alveolus to vascular sheath. The gradient is a direct result of the overdistention, which has the effect of pulling away the enveloping alveoli from the pulmonary blood vessels, and so of diminishing the pressure in the sheaths around them.

The sites of the ruptures may be indicated by the injection of hot gelatin containing particles of carmine of small size into the bronchial tree of a collapsed lobe which has immediately before been forced to leak air by experimental overinflation¹⁴. This zone of overinflation in the animals lay immediately around the tip of the catheter from which the air issued. The pressure registered on the mercury manometer during the insufflation, from 1 to 22 cm. of mercury, was somewhat higher than that to which the alveoli were actually exposed, for there was some reflux, due to the fact that the tip of the catheter was loosely inserted. In sections cut from this material, properly fixed, the carmine particles appeared in small heaps on the air side of the alveolar wall, where they had been filtered out as the fluid gelatin passed through the minute ruptures into the underlying vascular sheaths. Where the ruptures were larger the carmine appeared in streams of particles leading from the sites of rupture into the mass of gelatin in the sheath, which had displaced, in part at least, the air which had invaded it but a short time before, during the first stage of the experiment. I have seen no cases of a single ruptured alveolus, such as have been said by some authors to be implicated possibly in such leakages.

Dangers from Atelectasis—In the experimental cases the region of enlarged volume, or alveolar ectasia, was centrally situated, around the tip of the catheter. It was ballooned by the blast of air. Around this focus was a zone where the air spaces must have been reduced in volume, to compensate for the central enlargement. But in cases in man, on the contrary, it is often the area of diminished volume, or atelectasis, which is centrally placed, while around it, or adjoining it, there is compensatory expansion of the air spaces, or, as it is often called, com-

14 Macklin, C. C. The Site of Air Leakage from the Lung Alveoli into the Interstitial Tissue During Local Over-Inflation in the Cat, *Anat. Anz.* 85: 78, 1938.

pensatory emphysema¹⁵ It is doubtless from this hyperexpanded region that the leakage of air occurs The importance of diminution in lung volume from any cause should therefore be stressed, for if the capacity of the thorax cannot be lessened to cover the reduction, there must necessarily be an expansion of lung substance to fill the space

Atelectasis thus assumes a baneful significance, for it engenders overstretching of the neighboring alveoli, with attendant danger of multiple rupture The literature is full of instances of pulmonic interstitial emphysema associated with bronchopneumonia A number of cases were reported during the great influenza epidemic of 1918, as those by Kelman¹⁶ and Clark and Synnott¹⁷ Thus, bronchopneumonia may be the basis of air leakage The influences of inflammation and toxemia probably weaken the alveolar bases, so increasing the likelihood of rupture In some of these cases atelectasis is insidious, yet even in cases in which no trace of it has been found I suspect its complicity⁴ More delicate technics for its detection may yet reveal reduction in pulmonic volume in all cases of interstitial emphysema of the lungs This reduction may be large, as in some instances of impaction by foreign bodies already alluded to or in cases of massive collapse of the lungs or of lobectomy without spatial compensation In all cases one may regard reduced volume in lung tissue as a potential cause of pulmonic interstitial emphysema

In the usual cases of pulmonic interstitial emphysema and pneumomediastinum in man there is no preceding insufflation of air as in the experimental animals, but there must be a descending pressure gradient from the area of alveolar ectasia to the tissue fluid spaces of the pulmonic vascular sheaths of the region The transport of air along the vascular sheaths is doubtless much slower and less spectacular than it is when air is actually being blown in Coughing probably facilitates the leakage It seems likely that the lengthening and shortening movements of the pulmonic blood vessels, associated with similar movements of the bronchi in respiration, serve to move the train of bubbles along through the vascular sheaths The danger of atelectasis from this angle should be

15 It would be desirable if pathologists and clinicians could establish a better nomenclature for the conditions known as "emphysema" This term is used for a simple distended state of the alveoli, as in "compensatory emphysema", for a degenerate condition of the alveolar walls associated with increased volume, as in "pulmonary emphysema," or "pulmonic parenchymatous emphysema" and for the totally different condition of air in the interstitial tissues, "interstitial emphysema" This application to more than one entity leads to much confusion

16 Kelman, S R Experimental Emphysema, *Arch Int Med* **24** 332 (Sept) 1919

17 Clark, E, and Synnott, M J Influenza-Pneumonia Cases Showing Gas in Fascial Tissues, *Am J M Sc* **157** 219, 1919

kept in mind by the clinician and measures taken to correct the condition of overinflation resulting therefrom, so that the leaking may be stopped. Among the recent reports is that of Graebner,¹⁸ who cited 3 cases in which air was demonstrated roentgenoscopically in the mediastinum. All the patients had acute obstructive laryngitis. One (7 years of age) had measles and pertussis, another (aged 16 years) had sore throat, a temperature of 104.8 F and evidence of infectious involvement of the lower part of the respiratory tract, and the third (aged 2½ years) showed signs indicative of marked bronchopneumonia, with a temperature of 105.2 F. Graebner postulated that the air reached the mediastinum from the pulmonary interstitial tissue. It seems evident that the ability of the alveoli to retain air was impaired, and that this was due to one or more of the following factors: obstructive laryngitis, possible atelectasis and weakening of the alveolar walls following the probable overstretching and effects of the infection. Escudero and Adams¹⁹ reported an interesting series of 9 cases of experimental spontaneous pneumothorax in dogs associated with massive collapse, and they added a single case of a similar condition in an 8 year old girl.

In some cases of pneumomediastinum and its sequelae in man, however, the mode of production is much like that in my experimental animals. Eisen²⁰ recently recorded a case of surgical emphysema, pneumothorax and pneumoperitoneum in a normal boy of 4 years, who, while being anesthetized with ether by the "closed" method, showed rapid pulse and respirations and evident generalized subcutaneous emphysema. The pressure of the ether vapor, passing through nasal catheters into the nasopharynx, was probably too high. Roentgenograms showed large amounts of air in the mediastinum, root of the neck and retroperitoneal tissues, there was some in the thighs and left pleural cavity. Eisen expressed the view that this air leaked out from the overinflated lung along the vascular sheaths to the mediastinum, in the way that I have described.² In such a case the generalized emphysema comes on rapidly, as in the experimental animals.

When one reflects on the matter, it seems marvelous that the alveoli are so perfectly air competent, the wonder is that they do not allow air to escape into the interstitial tissues more frequently. It seems, however, as though some persons are constitutionally liable to air leakage and suffer repeated attacks. Recurrent seizures of spontaneous

18 Graebner, H. Pneumopericardium and Pneumomediastinum in Cases of Acute Obstructive Laryngitis, *Arch Otolaryng* **29** 446 (March) 1939.

19 Escudero, L., and Adams, W. E. Spontaneous Pneumothorax Associated with Massive Atelectasis. An Experimental and Clinical Study, *Arch Int Med* **63** 29 (Jan) 1939.

20 Eisen, D. Surgical Emphysema, Pneumothorax and Pneumoperitoneum. A Roentgenographic Study of a Case, *Radiology* **31** 623, 1938.

pneumothorax, such as Hamman⁵ recorded in his case 4, seem to me to be sequelae of such leakages. It may be possible, too, that the propensity to pulmonic air leakage is hereditary, since a number of cases have been reported in which more than one member of a family has been affected, and in which there was no obvious disease to explain the leakage.²¹

This is not the place to expatiate on the occasionally fatal ending in cases of mediastinal emphysema, but the literature contains a number of such instances. The importance of the roundabout route of air transit from the alveoli to the mediastinum along the vascular sheaths grows in the mind of the reader of these reports. Leveuf and Kohn²² reported a case of mediastinal and subcutaneous emphysema in a child of 2½ years in whom release of the air through an incision at the base of the sternum led to a prompt and permanent recovery.

SUMMARY

1 Air may break through from overdistended alveoli of the lung into the underlying pulmonic perivascular sheaths and travel along these sheaths in channels which it makes to the mediastinum.

2 In so doing it presses on the pulmonic blood vessels and interferes with the flow of blood in the part, not only of the incoming arterial but also of the venous blood.

3 Because the air which has invaded the interstitial tissue from a local part crowds into the sheaths of the larger blood vessels at the root of the lung, its obstructive effect becomes more general, creating an impediment to the pulmonic blood flow over a wide area. The blockade of the pulmonary blood stream may have serious consequences.

4 This method of transport of air from alveoli to mediastinum along the vascular sheaths has been demonstrated convincingly in experimental animals in which air was blown through a urethral catheter into a local part of the lungs. The evidence is from fresh lungs of these animals, particularly from properly fixed and sectioned material taken from them. The same air-tunneled vascular sheaths have been noted in the human lung.

5 Clinically this transport of air and resultant circulatory impediment may occur when a region of alveolar overdistention arises. The common cause is local diminution in volume of lung substance. This reduction in volume may be relatively small, as in the common type of atelectasis, and may be multiple. Or it may be large, as in massive collapse or surgical removal of a lobe without operative compensatory

21 Göttsche, C. Spontaneous Pneumothorax. Five Cases in the Same Family, *Ugeskrift for Læger* **95** 765, 1933.

22 Leveuf, J., and Kohn, R. Emphyseme sous-cutané et médiastinal spontané chez l'enfant, *Arch de méd d enf* **41** 156, 1938.

spatial reduction. The leakage of air into the vascular sheaths may be prolonged over some time, with corresponding continuation of the transport of air and its evils.

6 The pneumatization of the pulmonic vascular sheaths can occur in the human subject by the development of too high an intrapulmonic pressure during the faulty administration of an anesthetic by the closed method.

7 The actual inlets for air to the sheath system are multiple and very small ruptures in the alveolar bases which overlie the finer ramifications of the pulmonary blood vessels. These openings are in the meshes between the capillaries. The alveoli so perforated are probably numerous and distributed over a comparatively wide area. No examples of grossly torn or ruptured alveoli were seen in the experimental animals.

8 Infections may similarly travel through the pulmonary interstitial tissue along the air-hollowed vascular sheaths, and give rise to infective foci along the way.

9 The only pulmonic interstitial emphysema which I have seen is that of the pulmonic blood vessels and extensions therefrom, such as those into the partitions of interstitial tissue which separate subdivisions of lung substance. In the light of this study, pulmonic interstitial emphysema becomes important because of (a) embarrassment to the pulmonary circulation, (b) spread of infection and (c) formation of subpleural blebs which extend from the sheaths along connective tissue trabeculae or partitions, and which may rupture and give rise to pneumothorax, as some writers have asserted. I have not yet observed such ruptured blebs, however.

10 This pathologic transport of air is dangerous also because it distends the mediastinum, so bringing further embarrassment to the circulation through pressure on the heart and great vessels. This may be fatal. Pneumomediastinum leads also to pneumoprecordium, with Hamman's sign, to interstitial emphysema of the opposite lung and hitherto unaffected regions of the same lung, to pneumoretroperitoneum (and even pneumoperitoneum) and extensions of emphysema to the groin and leg, and to emphysema of the connective tissues of the neck, head, arm, chest and abdomen. These extensions from the mediastinum have a salutary feature, inasmuch as they relieve the distress of the circulation within the mediastinum. Abatement of mediastinal pressure results also when the mediastinal wall ruptures, giving rise to pneumothorax. This also has the effect of closing the leaks.

11 Though in many clinical cases of generalized interstitial emphysema originating in this way from pulmonic leaks the condition clears up of itself in a week or two, there seem to be cases in which operative

intervention may be required for (a) relief of mediastinal and intrapulmonic pressure, which may threaten life through interference with the circulation, and (b) stoppage of the leaks. The first is accomplished by mediastinotomy and suction, the second, by artificial pneumothorax.

12 There seems to be a group of people who are constitutionally prone to leakage of air of this type from the lung. Susceptible persons may have repeated attacks. The same applies to spontaneous pneumothorax, which seems to be causally associated.

The brief list of references in this article contains only articles which have been specially selected to illustrate outstanding points. The literature pertaining to the various aspects of emphysema in the mediastinum and related parts is enormous and is growing rapidly. Many of the citations made here contain bibliographies. Treatises, such as that of Graham, Singer and Ballou (*Surgical Diseases of the Chest*, Philadelphia, Lea & Febiger, 1935), contain ample lists of references.

Mr. Walter Downs aided in the preparation of the material and photographs, and Dr. Madge Thurlow Macklin gave constant help in this study.

STUDIES ON "ESSENTIAL" HYPERTENSION

I CLASSIFICATION

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AND

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Arterial hypertension¹ is a common phenomenon. In some instances it is associated with diseases already plentifully described and believed to cause it. Such conditions comprise disturbances of four main systems: the genitourinary, the nervous, the endocrine and the vascular. It is generally believed that when disorders of these systems are accompanied by arterial hypertension the hypertension is a dependent phenomenon, for when they are relieved it often disappears. Such varieties of secondary arterial hypertension (*B*, table 1) are present in only a small number of all cases in which diastolic pressure is elevated. When none of these diseases is present and arterial pressure is elevated, an independent disease called "essential" (or "idiopathic") hypertension is regarded as responsible for the pathologic processes observed. Although the expression is an admission of ignorance, it must be understood that the condition called "essential" hypertension is present in over 85 per cent of all cases in which blood pressure is elevated.²

"Essential" hypertension itself has been regarded as a syndrome for which any one of a number of different diseases may be responsible. Fishberg³ stated:

It seems highly probable, in fact almost certain, that essential hypertension is merely a collective concept—for a number of conditions having in common the

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1 When the term "arterial hypertension" is used in this study it is intended to mean elevation of both systolic and diastolic pressures.

2 (a) Keith, M. M. Classification of Hypertension and Clinical Differentiation of the Malignant Type, *Am Heart J* 2: 597 (Aug) 1927. (b) Adson, A. W., and Allen, E. V. Essential Hypertension. I. General Considerations, *Proc Staff Meet, Mayo Clin* 12: 1 (Jan 6) 1937.

3 Fishberg, A. M. Hypertension and Nephritis, ed 3, Philadelphia, Lea & Febiger, 1934.

positive characteristic of arterial hypertension and the negative one of the absence of primary renal disease

An attempt at classifying cases of "essential" hypertension is one method of testing the value of this idea. The condition has been treated nosologically a number of times, usually from the point of view of its severity, its rate of progress or the state at which the process has arrived.² Kahler⁴ attempted a physiologic analysis.

The classification now proposed for cases of "essential" hypertension is the outgrowth of the observation that the wide variety of clinical disturbances associated with this condition can, for the most part, be divided into the same four groups (*C*, table 1)—renal, neurogenic, endocrine and vascular—as the diseases to which arterial hypertension is commonly thought to be secondary. Further evidence for the soundness of this grouping of cases of "essential" hypertension is the fact that an elevation of arterial pressure can be produced experimentally in animals by disturbance of one or other of at least three of these same four systems (*A*, table 1)—the urinary, the nervous and the vascular. It is not yet certain whether it can be brought about by disturbance of the endocrine system. The mechanisms of the three types of disturbances are still imperfectly understood, but it is important that in many respects they appear analogous to those of similar disturbances in human beings. The classification is, for these reasons, physiologic.

Neither lesions resulting from prolonged arterial hypertension (as indicated in cardiac failure, renal failure or apoplexy) nor symptoms and signs believed to be dependent on hypertension (palpitation or headache) have been used as a basis for classification, although occurrence of these symptoms and signs has been used to distinguish the various groups in point of behavior.

In making this classification, 218 cases of "essential" hypertension studied in this hospital during the past ten years were reviewed. At the time of writing, 90 of the patients are dead, of 11 there is no information, and 117 are living. The progress of 114 continues to be studied. All were referred as having typical "essential" hypertension and either exhibit or have exhibited elevation of diastolic pressure without failure of renal function. In most cases the time of the onset of hypertension is known within two years.

4 Kahler, H. Die Blutdrucksteigerung, ihre Entstehung und ihr Mechanismus, *Ergebn d inn Med u Kinderh* 25: 265, 1924.

TABLE 1—*Analysis of Arterial Hypertension (Elevation of Diastolic Pressure) According to the Four Systems Affected by the Associated Disturbances*

I Renal Parenchyma	II Nervous System	III Endocrine System	IV Arterial Vascular System
A Experimental Lesions Resulting in Hypertension in Animals			
Roentgen sclerosis of kidneys ^a	Removal of carotid sinus and aortic depressor nerves ^b	Injectations of estrogen and pitressin (beta hypophamine) resulting in renal lesions like those found in eclampsia (blood pressure not stated) ^b	Partial constriction of renal artery ^c
Chemical nephritides (oxalate) ^b	Intracerebral injection of kaolin ^b		High intake of vitamin D and cholesterol ^b
Serum nephritis ^c	Hypothalamic injury ^d		
Reduction of renal substance ^d	Increased intracranial pressure ^d		
Constriction of renal vein ^e			
Ureteral ligation ^f			
B Lesions Associated with Hypertension in Man (partly after Fishberg)			
Renal diseases with renal failure	Tumors of brain, etc., giving rise to increased intracranial pressure	Pituitary basophilism	Obstructive arteriosclerosis of renal artery ^h
Glomerulonephritis (especially chronic)	Diseases of the brain stem (bulbar poliomyelitis, etc.)	Tumors of adrenal glands	Periarteritis nodosa of renal artery
Urinary obstruction		Tumors of ovary (arrhenoblastoma)	Coarctation of aorta ^o
Polycystic kidneys		Ovarian hypofunction (?)	Lead poisoning
Necrotizing nephroses			
Suppurative nephritis (rare)			
Pyelonephritis			
C Clinical Phenomena Associated with So Called Essential Hypertension			
Renal Diseases without renal failure or antecedent hypertension	Diencephalic syndrome	Disturbances of the endocrine system	Arteriosclerosis
(Renal hypertension)	(Nervous hypertension [?])	(Endocrine hypertension [?])	(Arteriosclerotic hypertension [?])

^a Hartman, I. W., Bolliger, A. and Doub, H. P. Experimental Nephritis Produced by Irradiation, *Am J M Sc* **172** 487 (Oct.) 1926

^b Arnott, W. M., and Kellar, R. J. Effect of Renal Denervation on the Blood Pressure in Experimental Renal Hypertension, *J Path & Bact* **42** 111 (Jan.) 1936

^c Arnott, W. M., Kellar, R. J., and Matthew, G. D. Hypertension Associated with Experimental Serum Nephritis, *Edinburgh M J* **44** 205 (April) 1937

^d Chanutin, A., and Barksdale, I. L. Experimental Renal Insufficiency Produced by Partial Nephrectomy Relationship of Left Ventricular Hypertrophy, Width of Cardiac Muscle Fiber and Hypertension in Rat, *Arch Int Med* **52** 739 (Nov.) 1933 Wood, J. E., Jr., and Ethridge, C. Hypertension with Arteriolar and Glomerular Changes in Albino Rat Following Sub Total Nephrectomy, *Proc Soc Exper Biol & Med* **30** 1039 (May) 1933

^e Pedersen, A. H. A Method for Producing Experimental Chronic Hypertension in the Rabbit, *Arch Path* **3** 912 (May) 1927

^f Harrison, T. R., Mason, M. F., Resnik, H. and Rainery, I. Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, *Tr A Am Physicians* **51** 280, 1936

^g Koch, E., and Mies, H. Chronischer arterieller Hochdruck infolge Dauerausschaltung der Blutdruckzügler, *Krankheitsforschung* **7** 241 (July) 1929

^h Dixon, W. E., and Heller, H. Experimentelle Hypertonie durch Erhöhung des intrakraniellen Druckes, *Arch f exper Path u Pharmacol* **166** 265 (June) 1932 Heller, H. Ueber die Reizempfindlichkeit der Blutdruckzentren und die experimentelle Erzeugung zentral bedingten Hochdrucks, *Klin Wchnschr* **13** 241 (Feb 17) 1934

ⁱ Walter, C. W., and Pijoan, M. J. Persistent Hypertension Due to Hypothalamic Injury Surgery **1**: 282 (Feb.) 1937

^j Cushing, H. Concerning a Definite Regulatory Mechanism of the Vasomotor Center Which Controls Blood Pressure During Cerebral Compression, *Bull Johns Hopkins Hosp* **12** 290 (Sept.) 1901

^k Byrom, F. B. Effect of Oestrogenic and Other Sex Hormones on the Response of the Rat to Vasopressin, *Lancet* **1** 129 (Jan 15) 1938

^l Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W. Studies on Experimental Hypertension Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J Exper Med* **59** 347 (March) 1934

^m Appelrot, S. Hypervitaminosis D and Blood Pressure in Dogs, *Am J Physiol* **105** 294 (Aug.) 1933 Handovsky, H. Chronic Hypertension in Dogs During the Oral Administration of Vitamin D, *J Physiol* **62** 63 (Aug.) 1937

ⁿ Goldblatt, H. Personal communication to the authors

^o Steele, J. M., and Cohn, A. F. The Nature of Hypertension in Coarctation of the Aorta, *J Clin Investigation* **17** 514 (July) 1938

The cases were divided into five main groups, as follows

I Renal Disease

- 1 Antedating the onset of arterial hypertension
 - (a) Symptoms or signs of organic renal disease of any nature
 - (b) History of pathologic urinary constituents
- 2 Probably antedating the onset of arterial hypertension
 - (a) Renal abnormalities not resulting from hypertension
 - (b) Lesions of chronic glomerulonephritis at autopsy (in a few cases)
- 3 Occurring after the onset of arterial hypertension
 - (a) Abnormal renal lesions not usually thought to be associated with or resulting from hypertension

II Disorders of the Nervous System

"Hypertensive diencephalic syndrome" of Page (see section II) without other classifying criteria

III Endocrine Dysfunction

Evidence of disturbance in the glands of internal secretion

IV Vascular Disease

- 1 Peripheral arteriosclerosis (in elderly persons) without criteria pointing to other classes
- 2 Severe arteriosclerosis in persons of any age, i e., calcification on roentgen or postmortem examination

V Unclassified

Conditions which cannot be classified according to any of the appearances mentioned and conditions on which data are insufficient for classification

Two hundred and eighteen cases are a small number for classification, especially when they seem, to a certain extent, selected, since the proportion in which hypertension developed before the age of 40 was extraordinarily large (68 per cent). The effort to test further the degree to which the hypertension in these cases is genuinely "essential" is nevertheless important and, we believe, rewarding. The various groups into which the cases fall will be discussed separately.

I ORGANIC RENAL DISEASE

In the recent literature a number of reports have appeared of cases in which arterial hypertension was associated with unilateral renal disease of various sorts. Removal of the affected kidney resulted in prolonged and dramatic decreases in arterial pressure in cases of pyelonephritis,⁵ adenocarcinoma (Wilms' tumor),⁶ partial constriction of a renal

5 (a) Butler, A. M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* **16** 889 (Nov.) 1937. (b) Baker, N. W., and Walters, W. Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis. Treatment by Nephrectomy, *Proc Staff Meet, Mayo Clin* **13** 118 (Feb 23) 1938.

6 Pincoffs, M. C., and Bradley, J. E. The Association of Adenocarcinoma of Kidney (Wilms' Tumor) with Arterial Hypertension, *Tr A Am Physicians* **52** 320, 1937.

artery⁷ and infarction of the kidney⁸ Also, the relation of chronic pyelonephritis⁹ and other diseases of the kidney¹⁰ to arterial hypertension has been emphasized These reports and those indicating that a variety of experimental renal disturbances appear to cause hypertension in animals¹¹ have made it seem necessary to examine the state of the kidneys in our cases Organic renal disease of any nature antedating or probably antedating the development of arterial hypertension was believed important from this point of view Cases in which various lesions of the kidneys were observed at autopsy have also been included There were 56 such cases (26 per cent)

The renal symptoms and signs encountered were numerous and various There were cases (6) in which acute nephritis was followed by arterial hypertension and what was considered to be normal renal function, cases (8) in which, post mortem, lesions typical of chronic glomerulonephritis were discovered in spite of the fact that the course of the illness was indistinguishable from that of essential hypertension, cases (8) in which, before the onset of hypertension, histories of attacks of renal calculus were given, cases (4) in which pyelonephritis antedated the onset of hypertension, in 3 of which pregnancy appeared as a complication, cases (2) in which bilateral hydronephrosis was present without renal insufficiency, a case (previously reported¹²) in which severe renal damage followed excessive use of alkalis and in which, three years later, hypertension was present with normal renal function, a case in which hypertension developed after an episode of nitrogen retention and albuminuria in consequence of a severe burn from a sun lamp, cases (8) in which there was a history of persistent albuminuria antedating the onset of hypertension, cases (5) in which there was persistent pyuria, and cases (13) in which miscellaneous renal lesions were noted of a type not usually considered to result from arterial hypertension (table 2)

7 Leadbetter, W F, and Burkland, C E Hypertension in Unilateral Disease, *J Urol* **39** 611 (May) 1938

8 Boyd, C H, and Lewis, L G Nephrectomy for Arterial Hypertension, *J Urol* **39** 627 (May) 1938

9 (a) Longcope, W T Chronic Bilateral Pyelonephritis Its Origin and Its Association with Hypertension, *Ann Int Med* **11** 149 (July) 1937 (b) Peters, J P, Lavietes, P H, and Zimmerman, H M Pyelitis in Toxemias of Pregnancy, *Am J Obst & Gynec* **32** 911 (Dec) 1936 (c) Zimmerman, H M, and Peters, J P Pathology of Pregnancy Toxemias, *J Clin Investigation* **16** 397 (May) 1937

10 Leiter, L Unusual Hypertensive Renal Disease, *J A M A* **111** 507 (Aug 6) 1938

11 A summary of the various methods employed for the production of experimental renal hypertension is given in table 1

12 Steele, J M Renal Insufficiency Developing During Prolonged Use of Alkalis Report of a Case, *J A M A* **106** 2049 (June 13) 1936

TABLE 2—Renal Disease

Case No	Sex	Patient History	Family History	Age at Onset, Years	Duration, Years	Symptoms When First Seen	Average Extremes of Blood Pressure, Mm Hg		Ocular Fundi**		Progress†	Present Status§	Other Classifying Signs#	Comment
							Highest	Lowest	Arterio sclerosis	Hemor rhage or fundate				
1	♂	J B	0	24	2	H+C	230/150	Acute Nephritis Before Onset	+	+++	CR	DR	0	Acute nephritis, at 23, with malignant course
2	♂	J L*	0	<24	>2	Ce	210/110	190/110	+++	+	0	DC	IV+	Same, with epilepsy
3	♂	J C*	0	27	11	0	200/140	190/120	0	+++	R	DR	IV+	Acute nephritis, at 27, calculus at 35
4	♀	A C	0	19	3	H	190/120	169/110	+	+	CR	DR	0	Acute nephritis, at 19, with malignant course
5	♀	D C	0	21	1½	C	250/160	210/140	0	++	CR	DCR	0	Same at 20
6	♀	S S	0	30	17	0	160/100	110/90	0	0	?	L	0	Scarlet fever and nephritis, at 70
7	♂	R J†	0	<26	>1	C	210/150	Glomerulonephritis at Autopsy						
8	♂	P M	0	22	2	H	210/130	170/130	0	+++	CR	DR	IV+	Malignant course
9	♂	G A	0	<27	>2	H	210/130	170/80	0	+++	R	DR	0	Malignant fever
10	♂	F W	0	33	7	0	230/110	180/105	++	+	R	DCR	IV+	Malignant course
11	♂	A B	+	30	12	H	250/160	220/130	++	+	CR	DR	IV+	Renal colic (?) calculus at 39
12	♂	E B	+	41	2	H	250/150	220/140	++	+	R	DCR	IV+	
13	♂	D H	+	37	2	H	260/190	230/120	0	+++	CR	DCR	0	Albuminuria, pyuria at 33
14	♂	H S	0	25	12	H	235/160	220/125	0	+++	Ce	DCe	0	Albuminuria at 22, 37
15	♂	P M†	0	23	1	H	270/170	220/120	+	+++	CR	DCR	IV+	
16	♂	D W†	+	23	7	H	210/140	150/100	0	++	0	I	II+	Calculus removed at 23
17	♂	I F	+	41	3	H	200/150	190/120	0	++	R	L	0	Calculi at 35, and later
18	♂	J C	0	55	5	0	200/140	170/120	0	++	0	L	II+	Calculus at 25, passed
19	♂	M H	0	31	10	H	200/120	160/110	0	0	0	L	0	Calculus removed at 45, passed at 48
20	♂	I M	+	<45	>1	0	210/130	180/125	+	0	R	D?	0	Calculus at 26, passed
21	♂	H S	+	34	2	H	270/160	265/110	+	++	CR	DC	IV+	Calculus at 39 and 40, passed
22	♂	L B	+	45	8	0	250/140	180/125	0	+	CR	DCR	IV+	Calculus and infection at 22 and 34, mild bilateral hydronephrosis
23	♀	H F	+	24	8	H	180/130	145/100	0	0	0	L	IV+	Calculi at 41 and later
24	♀	M F	0	29	7	H	260/140	220/120	0	+++	R	DR	0	With pregnancy at 21
25	♀	M P	+	29	10	H	300/160	230/130	+	+	Ce	L	IV+	With pregnancy at 18 and 24
26	♀	A L	0	33	1	0	260/170	210/150	±	+	CR	DR	0	With pregnancy at 29
27	♂	L W	0	26	1	0	230/150	210/130	0	+	R	DR	IV+	At autopsy
28	♂	H A	0	<47	>1½	C	185/110	150/100	+	0	R	DR	IV+	Congenital cystic kidney, left
29	♂	H A	0	28	9	0	280/170	240/150	0	+++	Ce	DR	IV+	Tuberculosis of kidney, unilateral
30	♂	J G	+	21	11	0	210/145	180/125	+	++	R	DR	IV+	Tuberculosis of kidney, unilateral
31	♂	M W	0	33	8	0	230/140	190/110	0	+	0	D	0	Moderate bilateral hydronephrosis
32	♂	A L	0	23	6	H	160/100	135/90	0	0	0	L	0	Calculi at 23, colic 6 times
33	♂	C J	+	58	2	0	220/150	200/130	0	+	0	L	0	Marked unilateral hydronephrosis
34	♂	L L	+	14	10	Ce	160/100	140/90	+	0	0	L	IV+	Renal damage after alkali at 52
35	♀	M B	+	24	9	H	180/125	170/115	±	0	0	L	IV+	Nephritis after sun lamp burn at 44
							200/130	175/105	0	0	0	L	0	Marked ptosis with pain

Possible Renal Disease—Albuminuria Before Onset									
36 ♂	F M	0	34	7	H C	260/150	200/130	0	++
37 ♂	R R	0	28	21	O	180/120	170/110	0	+
38 ♀	C T	0	31	16	H C	210/120	160/115	+	+
39 ♀	E Z	0	45	12	H C	200/130	180/105	+	0
40 ♂	R B	0	<45	>5	H	200/110	240/115	+	+
41 ♂	H M	0	<39	'	0	160/100	150/90	+	+
42 ♂	W M	+	47	7	H C	200/120	170/110	+	+
43 ♂	B R	+	50	15	0	230/130	190/110	+	+
Possible Renal Disease—Miscellaneous									
44 ♂	F E	+	40	7	H C	230/140	200/120	+	+
45 ♂	J O	0	32	2	0	230/110	190/130	0	0
46 ♂	O G	+	34	7	C	190/120	155/100	+	0
47 ♂	J D	+	21	10	H	160/90	115/85	0	0
48 ♂	J K	+	29	9	H	230/170	230/130	0	+
49 ♂	F M*	0	17	9	C Ce	230/135	185/130	0	+
50 ♂	A R	+	30	16	H C	280/190	220/160	+	+
51 ♂	J C	0	36	4	H	280/150	250/110	+	+
52 ♂	M M	+	34	5	H	170/120	145/100	0	0
53 ♂	P F	+	36	8	H	150/85	130/80	0	0
54 ♂	A F	0	33	11	0	210/130	180/120	0	0
55 ♂	H K	0	24	3	0	240/160	200/140	0	0
56 ♂	H E	0	42	14	0	220/115	200/110	+	0
Summary		36%+	Average 33.4 yr	Average 7.6 yr	54% H 35% C	221/138	190/117	43%+	65%+
				69 D					62% D (76% with renal failure)

* Cases previously reported¹³

† Cases previously reported^{20b}

‡ ++ = hypertension in family of one parent, ++ = hypertension in family of both parents

§ Age at which hypertension was first discovered Unless so indicated, the blood pressure is known to have been normal within two years previous to this age The age of onset is known, in many cases, within one year

|| To the present (1938) or to death

¶ Symptoms H = headaches, C = cardiac insufficiency or pain, Ce = cerebral vascular "spasm," apoplexy, transient paralyses or "hypertensive encephalography", zero = none

†† The figures given indicate the approximate highest and lowest levels of both systolic and diastolic pressure, measured over a period of several days for each Single extreme readings are not given Measurements within a year following neurosurgery are not given

** Arteriosclerosis—i e, tortuosity of vessels, narrowing, increased light reflex, arteriovenous constriction Hemorrhage, or evolute—i e, perivascularitis, scars, evolute, fresh and old hemorrhage, papilledema

†† O = cardiac failure or coronary accident, R = renal failure or insufficiency, moderate or severe, Ce = apoplexy, "spasm," paralysis, or hypertensive encephalopathy

§§ L = living, D = dead, C = cardiac failure or coronary accident, R = renal insufficiency, A = apoplexy, ? = unknown

When one or more of the criteria for classifying the case in another group are present, this is indicated These criteria are graded from + to ++++, and indicate cases with the significant findings of two groups only when graded ++++ or ++++

Of the patients in this group 44 were males and 12 were females. Thirty-four died, the average duration of their disease being six and nine-tenths years. Twenty-four died of renal failure or of renal and cardiac failure together, 4 primarily of cardiac failure, 3 of cerebral accidents and 1 of anuria following a cystoscopic examination. The manner of death in 2 instances is unknown. Fifteen patients lived four years or less after the onset of hypertension. Reports of 2 cases as examples follow.

CASE 3 (table 2) —J C¹³ was a 38 year old Italian subway worker. His past history was irrelevant. There was nothing in his family history to account for the presence of hypertension. At the age of 27 he had an infection of the upper respiratory tract, which was followed by edema of the face and ankles, dyspnea and scanty output of urine. He entered the St. Francis Hospital, where a diagnosis of acute nephritis was made. The systolic blood pressure was 190 mm of mercury and the diastolic was 100. There were edema, albuminuria, hematuria and fever. After he had been at rest in bed a month, edema disappeared and the blood pressure fell to 150 systolic and 85 diastolic. He was discharged, although albuminuria persisted. He was well until the age of 35 when he had a sudden pain in the region of the right kidney, followed by pain on urination. On cystoscopic examination at the Fordham Hospital a renal calculus was not found. His symptoms subsided. The systolic pressure was 240 and the diastolic pressure 138. There were many white and red blood cells in the urine. A few months later (July 1935) he was referred to this hospital because of the development of palpitation and dizziness.

The tonsils were chronically inflamed. At the cardiac apex a systolic murmur was heard. The peripheral arteries were moderately thickened. The ocular fundi were normal except for arteriolar constriction. The heart was not enlarged on roentgen examination. The arterial systolic pressure, measured almost daily for a month, averaged 210, and the diastolic pressure 130. By the standard Van Slyke test urea clearance was 101 per cent of normal, and the kidneys after fluid had been withheld for twenty-four hours were able to concentrate urine to a specific gravity of 1.027. There was no albuminuria and no abnormal increase in the microscopic elements.

On October 14 both splanchnic nerves were resected above the diaphragm. The course of the disease apparently was not influenced. For two years the condition of the patient remained unchanged except for a rise in blood pressure to 260 systolic and 150 diastolic. Hemorrhages and exudate appeared in the ocular fundi.

In May 1938 a second attack of pain referable to the right kidney occurred, which was followed by hematuria and passage of "gravel." The urea clearance¹⁴ then had fallen to 49 per cent, and the maximal concentration of the urine¹⁵ showed a specific gravity of 1.022. Renal function soon became rapidly reduced, many hemorrhages were found in the retina, and five months later retention of

13 This case has previously been reported (Page, I. H., and Heuer, G. J. The Effect of Splanchnic Nerve Resection on Patients Suffering from Hypertension, *Am J M Sc* **193** 820 [June] 1937).

14 By "urea clearance" is meant the value obtained by application of the standard Van Slyke test.

15 By "maximal concentration of the urine" is meant the nonprotein specific gravity of the urine after fluids have been withheld for twenty-four hours.

nitrogen was discovered. The patient died of uremia in November 1938. Autopsy showed chronic glomerulonephritis, generalized arteritis and hypertrophy of the heart.

Summary—An attack of acute nephritis was followed some time later by persistent arterial hypertension with normal renal function. The clinical appearance was typical of "essential" hypertension until six months before death. At autopsy the lesions of chronic glomerulonephritis were observed.

CASE 30 (table 2)—J. G., a 31 year old unemployed man, had had albuminuria for as long as he could remember. He passed an examination for life insurance, however, at the age of 20. One year later the blood pressure was 180 systolic and 110 diastolic. In 1931, at the age of 24, the systolic pressure was 150 and the diastolic pressure 100. The patient complained of few symptoms referable to hypertension until the age of 28, when fatigue and palpitation appeared. The blood pressure was then said to be very high. At 29 the systolic pressure was found (at the Brooklyn Hospital) to be 220 and the diastolic pressure 110. Various tests of renal function were said to have given normal results. He was first seen in this clinic in May 1936.

The physical examination gave essentially negative results. The vessels of the fundi were somewhat tortuous. The heart was shown slightly enlarged in the roentgenograms. The results of numerous urea clearance tests varied markedly, indicating a range of from 75 to 176 per cent of normal. The maximal specific gravity of the urine was 1.023. The excretion of protein in the urine was usually very slight but on one occasion amounted to as much as 1.97 Gm. in twenty-four hours. The systolic pressure, recorded almost daily for a month, ranged between 228 and 190 and the diastolic pressure between 130 and 100, the lower figures having been observed after prolonged rest in bed. The blood pressure rose to a higher level during the next two and one-half years, usually varying between 140 and 150 diastolic. A significant change in renal function did not occur, although the size of the cardiac shadow increased slightly.

On intravenous injection of 20 cc. of diodrast, pyelograms disclosed the presence of bilateral hydronephrosis of moderate degree with constriction at the ureteropelvic junction. Proteinuria was greater when the patient was out of bed. Cystoscopic examination in November 1938 confirmed the diagnosis of bilateral hydronephrosis, most marked on the right, with angulation of the ureter. The patient died of anuria after examination.

Summary—Albuminuria persisted for many years. The onset of hypertension was placed at the age of 21. There existed, at the same time, bilateral hydronephrosis, probably due to a congenital renal abnormality. Except for this important lesion, the clinical appearance was that of "essential" hypertension.

II DISORDERS OF THE NERVOUS SYSTEM

In 1935, Page¹⁶ described a symptom complex occurring in young women suffering from essential hypertension which he called the "hypertensive diencephalic syndrome." Characteristic of this disease are attacks of (1) curious, irregular, blotchy blushing, first of the face, then spreading to the neck, the trunk and sometimes the abdomen, (2) spontaneous crying or watering of the eyes, (3) excessive perspiration,

¹⁶ Page, I. H. A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, *Am J M Sc* **190** 9 (July) 1935.

TABLE 3 —Hypertensive Diencephalic Syndrome ##

Case No	Sex	Patient	Family History	Age at Onset, Years	Duration, Years	Symptoms When First Seen	Average Extremities of Blood Pressure, Mm Hg		Ocular Fundi**		Progress††	Present Status§	Other Classifying Signs#	Comment
							Highest	Lowest	Arterio sclerosis	Hemor rhage or Exudate				
Diencephalic Syndrome—Marked														
1	♀	R H †	0	16	6	H	180/130	140/ 90	0	0	0	L	0	Marked emotional tension
2	♀	B H †	†	24	11	0	230/140	160/110	0	0	0	L	0	Onset with pregnancy
3	♀	M L †	0	22	14	0	270/160	190/130	0	0	0	L	0	Onset with pregnancy
4	♀	C D	0	28	13	H	220/120	190/110	0	0	0	L	0	Onset with pregnancy
5	♀	R D	0	28	11	H	250/160	190/120	0	+++	R	D R	0	Onset with pregnancy
6	♀	M C *	++	37	13	H	230/120	190/100	0	0	0	L	0	Onset with pregnancy
7	♀	A R †	0	23	7	H	230/140	180/120	0	0	2R	L	0	
8	♀	L R	+	39	11	0	270/115	200/100	+	0	2R	L	0	Epileptiform convulsions
9	♀	T L	0	33	8	H	210/130	165/ 95	+	+	0	L	0	
10	♀	M S *	0	32	5	H	220/140	200/120	+	0	0	L	IV+	
11	♀	E B	0	19	10	H	220/140	160/100	0	0	0	L	0	Epilepsy and rheumatic heart
12	♀	M O *	0	22	6	H	200/130	180/120	0	0	0	L	0	
13	♀	I I R	++	42	3	0	190/115	160/ 95	0	0	0	L	0	Cerebral hemangioma
14	♀	S I	++	<30	>7	H	250/140	190/110	+	0	0	L	0	
15	♀	E C	+	26	20	H	250/140	185/100	+	0	Ce	L	0	
16	♂	M S	+	18	21	H	210/130	170/110	0	0	0	L	0	Marked emotional tension
17	♂	L R	0	32	11	0	165/ 90	140/ 85	+	0	0	L	0	
18	♀	A L	0	22	8	H	230/130	180/120	+	0	0	L	0	
Diencephalic Syndrome—Moderate														
19	♀	G F	0	20	4	0	200/130	170/100	0	0	0	L	0	Bell's palsy at 22
20	♀	I S †	0	22	6	0	190/120	150/ 90	0	0	0	L	0	Marked emotional instability
21	♀	F S †	0	32	7	H	230/140	190/110	0	0	0	L	0	
22	♀	S H	+	<38	>13	H	220/115	185/ 90	+	0	0	L	0	
23	♀	J T	0	17	15	0	270/110	185/125	+	0	0	L	0	

24	♀	A R	0	39	9	0	220/115	153/100	+	0	?Ce	L	IV++	
25	♀	G L	+	34	4	H	200/130	150/90	0	0	0	L	I+	Ptosis of kidney
26	♀	M B	0	<39	>3	0	175/110	145/95	+++	+	0	L	0	
27	♀	M M	0	25	5	H	235/90	210/70	?	?	0	L	0	Onset with pregnancy, aortic in sufficiency
28	♀	I Z	0	<38	>6	C	250/130	210/115	+	0	C	L	0	Cardiac pain
29	♀	B L	+	42	18	H	250/110	180/90	+	0	C	L	IV+	Late onset
30	♀	S D	+	38	11	0	170/105	130/90	0	0	0	L	0	Onset with pregnancy
31	♂	S F	0	26	7	H	185/100	145/85	0	0	0	L	0	Marked emotional tension
32	♂	H S	0	28	2	H	220/130	165/110	0	0	0	L	0	Epilepsy
33	♂	G V†	0	18	6	0	230/150	170/120	0	0	0	L	0	Postoperative paraplegia
34	♂	I S†	+	33	8	H	250/150	170/100	0	0	C	D G	IV+	Died coronary occlusion (post-operative)
35	♀	D S†	0	34	5	0	290/160	210/120	+	++	0	D	0	Died of meningitis (postoperative)
36	♀	M W	+	19	3	0	260/150	215/125	0	+++	R	D R	0	Malignant course
37	♀	S J	0	<38	>2	C	290/170	240/110	+	++++	C R	D C R	IV+	Malignant course
Miscellaneous with Diencephalic Syndrome														
38	♀	A B	+	25	4	H	220/140	150/100	0	0	0	L	I+++	Renal colic with hematuria at 20
39	♀	H B	+	36	16	H	195/115	170/100	+	0	0	L	I++ IV+	Marked ptosis of right kidney
40	♀	G F	+	19	4	H	190/100	150/80	0	0	0	L	0	Congenital abnormality of spine with paroxysmal hypertension
41	♀	J O	0	39	12	H C	290/160	240/120	+	0	0	L	IV++	Onset with pregnancy, marked calcification of skull
42	♀	T F	+	36	?	H	220/130	170/105	0	0	?	L	0	Not well followed
43	♀	L R	++	22	5	H	200/120	180/100	0	0	0	L	0	Not well followed
44	♀	F B	+	25	10	0	270/160	230/110	+	+	0	?	0	Not well followed
45	♀	J A	++	19	?	H	220/140	170/120	+	0	?	?	III+	Not well followed
46	♂	B N	0	33	10	H	200/140	180/110	±	0	0	L	IV++	Not well followed
Summary		41%+	Average	Average	Average	62% H	Average	Average	42%+	16%+		11% D		
			28 1 yr	9 0 I	6% C		227/134	177/107						
				58 D										

For explanation of symbols and abbreviations, see footnotes to table 2

often at the site of the blush, (4) palpitation of the heart and increase in the cardiac rate, (5) rise in blood pressure, and (6) coldness of the extremities. Attacks are usually brought on by emotional stimuli but may arise spontaneously. Page pointed out the clinical similarity of this syndrome to "diencephalic autonomic epilepsy," described by Penfield¹⁷. Crisler and Allen¹⁸ have recently reported 4 similar cases, in 1 of which the blood pressure was approximately normal.

We have included in this group patients without evidence of renal lesions of endocrine disturbance who have the following signs and symptoms: (1) vasomotor instability, as evidenced by a tendency to blush, flushing, rapid changes in the level of the blood pressure, dermatographia, coldness of the extremities and attacks of palpitation, (2) emotional instability, as evidenced by spells of spontaneous crying, excessive nervousness and labile temperament, (3) autonomic instability, as evidenced by excessive perspiration, salivation and lacrimation, and (4) arterial hypertension. These symptoms, or some of them, are found usually in young women but occasionally in males and in older women. In addition, a history of sexual difficulties is often obtained, either of frigidity or of excessive desire.

Twenty-seven patients¹⁹ exhibited all these signs and symptoms. Nineteen others were subject to most of them and should probably be included in the same class. In this group of 46 only 5 are dead at the time of writing, 2 having died after operation. The average duration of the disease in those still living is nine years, 18 having lived more than ten years. Evidence suggestive of failure of the heart or kidneys has occurred in only 2. Significant changes in the eyegrounds are rare (table 3).

For the current purpose the use of this designation seems suitable, the symptoms being sufficiently distinctive. Eventually it may become desirable to distribute some of these cases among the other groups.

CASE 15 (table 3)—E. C., a 44 year old woman, a chef, had been known to have hypertension for twenty years. Her mother, two maternal uncles and a cousin died of this complaint, and two sisters were said to exhibit it. As a child, she had scarlet fever and diphtheria. She had always been moody, overexcitable, impulsive and of a worrying nature. She had been married and divorced twice. At the age of 25 a salpingo-oophorectomy was performed on the left side because of disease in the organs of the pelvis. (This condition had not influenced the menses.) Shortly afterward she began to complain of nervousness and irritability. She began to notice spells of spontaneous crying, palpitation, blushing, cold hands and feet and excessive perspiration. The blood pressure was 160 systolic. She

17 Penfield, W. Diencephalic Autonomic Epilepsy, *Arch Neurol & Psychiat* 22 358 (Aug) 1929.

18 Crisler, G. R., and Allen, E. V. The Flushing Syndrome Simulating "Diencephalic Stimulation" and Its Relation to Essential Hypertension, *Proc Staff Meet, Mayo Clin* 12 219 (April 7) 1937.

19 Five of these cases are dealt with in Page's original report¹⁶.

subsequently worked in various hospitals as a cook, and fairly good records were available of her blood pressure. At the age of 29 it was 160 systolic and 100 diastolic, at 30 it varied from 215 to 160 systolic and 105 to 90 diastolic, and from then to the age of 35 it fluctuated between 230 and 180 systolic and 150 and 100 diastolic. Marked lability when the pressure was at a higher level was still present three years later, and a four year record showed fluctuations between 270 and 180 systolic and 150 and 115 diastolic. Since the age of 34 she had noticed an increase in blushing, perspiration, coldness of the extremities and spells of spontaneous crying. At 41 she suffered an attack of "hypertensive encephalopathy" and one year later a similar attack. Headaches became more prominent and at times were incapacitating, although for the most part she was able to continue her work. At 43, examination disclosed extreme lability of the blood pressure, the values varying between 260 and 185 systolic and 135 and 100 diastolic, moderate sclerosis of the vessels of the retina, slight enlargement of the heart in roentgenograms, and a curious blotchy blush appearing on the neck and face as a result of emotional disturbance or during examination. The hands and feet were cold, mottled and often cyanotic, and perspiration was excessive. The maximal specific gravity of the urine was 1.024, and the urea clearance on two occasions was 93 and 78 per cent of normal respectively. The basal metabolism on several tests was within normal limits. The urine was normal.

She had one further attack characterized by cerebral symptoms, for which she entered the hospital. The blood pressure remained labile.

Summary—At the time of writing, this patient has been suffering from arterial hypertension and the "hypertensive diencephalic syndrome" for twenty years. Cerebral symptoms are beginning to appear. There is little evidence of damage to the heart or the kidneys. The extreme lability of the blood pressure is noteworthy.

III ENDOCRINE DYSFUNCTION

That endocrine disturbance plays a role in hypertension has seemed possible to investigators for many years. Malfunction of the pituitary gland, in particular, has been seriously considered as an important factor. Basophilic infiltration of the posterior lobe has been described a number of times,²⁰ but its importance remains undetermined. A number of syndromes of endocrine dysfunction with hypertension have been reported. Reisman²¹ in 1919 described "non-goitrous thyrotoxic hypertension," and Mannaberg²² also noticed such a condition. Boas and Shapiro²³ reported 27 cases of this condition, pointing out certain notable clinical characteristics—that the basal metabolic rate was often

20 Leary, O. C., and Zimmerman, H. M. Basophil Infiltration in the Neurohypophysis, *Am J Path* **13** 213 (March) 1937.

21 Reisman, D. Hypertension in Women, *J A M A* **73** 330 (Aug. 2) 1919.

22 Mannaberg, J. Arterieller Hochdruck und gesteigerter Grundumsatz, *Wien klin Wchnschr* **37** 84 (Jan. 24) 1924.

23 Boas, E. P., and Shapiro, S. (a) Diastolic Hypertension with Increased Basal Metabolic Rate, *J A M A* **84** 1558 (May 23) 1925, (b) Further Observations on Patients with Hypertension and Increased Basal Metabolic Rate, *Am Heart J* **1** 643 (July) 1926.

TABLE 4—*Endocrine Dysfunction* ##

Case No	Sex	Patient	Family History	Age at Onset, Years	Duration, Years	Symptoms When First Seen	Average Extremities of Blood Pressure, Mm Hg		Ocular Fundi**		Progress††	Present Status§§	Other Classifying Signs#	Comment		
							Highest		Lowest						Arterio sclerosis	Hemorrhage or Exudate
"Nongonitrous Thyrotoxic Hypertension"																
1	♀	M W	+	31	8	H	270/160	250/140	+	++	C Ce	D Ce	II+++++ B M R III + 29, onset with pregnancy			
2	♀	M G	0	31	9	H	210/150	150/100	0	+++++	0	L	II+++++ B M R + 27, onset with pregnancy			
3	♀	T G *	0	34	7	II	210/120	170/110	±	0	0	L	II+++++ B M R + 25, onset with pregnancy			
4	♀	M S	0	30	8	H	230/140	210/110	+	0	0	L	II+++++ B M R + 33, onset with pregnancy			
5	♀	D B	+	20	1	C	250/190	230/150	0	+++++	C Ce	D C Ce	II+++++ B M R + 35			
6	♀	J B	0	20	3	H	270/160	200/120	++	++	C R	D C R	II+++++ B M R + 35			
7	♀	M K	+	<32	>1	H	240/170	200/110	+	++	0	D C	II+++++ B M R + 37			
8	♀	L H	0	30	1	H C	260/170	200/110	++	++	C R	D C R	0 B M R + 34			
9	♀	B H	+	<30	>1	II C	240/110	220/130	0	+	C R	D C R	0 B M R + 24			
10	♀	I P	+	42	7	Ce	230/140	190/115	+	0	Ce	L	IV+ B M R elevated, onset with menopause			
11	♀	G A	+	40	6	H C	240/150	210/110	++	+	C R	D C R	IV++ B M R + 20 obesity worst with pregnancy, pituitary basophila			
12	♀	S T	0	23	13	H	240/125	180/120	0	+	0	L	0 B M R + 20 obesity onset with pregnancy			
13	♀	M P	0	<40	>2	H	260/115	200/100	++	0	0	D C	II+++++ B M R + 55			
Hyperthyroidism Before Onset																
14	♀	R S	+	<18	>4	0	250/130	210/110	0	0	0	L	II+++++ B M R + 21 Operation for nodular goiter obese			
15	♀	K I	0	42	9	H	220/140	170/110	+	0	0	L	II++++IV+ Exophthalmic goiter at 39, B M R + 52, now normal			
16	♀	D D	0	19	16	Ce	260/150	190/125	0	0	Ce	L	II++ Thyroidectomy for exophthalmic goiter at 24, B M R now normal			
17	♀	J Z	0	38	5	II C	220/130	210/120	0	±	0	L	0 Thyroidectomy for exophthalmic goiter at 32, B M R now normal			
18	♀	I A	+	30	10	II C	240/110	200/130	+	0	?	D ?	0 Exophthalmic goiter treated, followed by obesity			
19	♀	D B	0	26	20	II	230/110	160/100	±	±	C R Ce	D R	IV+++++ Exophthalmic goiter at onset with recovery			
20	♂	J P	0	37	7	II	230/110	170/100	0	0	0	I	II++ Exophthalmic goiter, thyroidectomy, 38			

markedly elevated without many of the signs of exophthalmic goiter and that thyroidectomy or administration of iodine had no effect on it. "Menopausal hypertension" has sometimes been considered a separate syndrome.²⁴ Fishbeig³ has observed hypertension following exophthalmic goiter and has also observed that it is associated with myxedema. It has often been noticed in cases of marked obesity. Herrick²⁵ reported the occurrence of the triad hypertension, obesity and diabetes.

The subjects of our own study were therefore examined for evidence of endocrine disturbance. This was found in 41 women and 2 men. In 13 patients it corresponded to the type described by Boas and Shapiro, the basal metabolic rates being elevated without obvious exophthalmic or nodular goiter. Seven patients gave histories of thyrotoxicosis antedating or appearing near the time of onset of hypertension. In 9 patients hypertension began at the menopause, 8 of these were obese. The onset in 4 was associated with rapid development of hypertrichosis. Three had many of the signs of Cushing's syndrome. Four were markedly obese. In others hypertension was associated with a variety of endocrine disturbances (table 4).

The diencephalic syndrome was prominent in 7 of the 13 patients with "non-goitrous thyrotoxic hypertension" and in 4 other patients with definite endocrine disturbance. Of the 43 patients in this group, 18 are dead at the time of this report. The cause of death was in 3, cardiac, in 5, cardiac and renal, in 2, renal, in 2, cerebral, and in 6 either unrelated to hypertension or unknown. Of the living patients still being studied (24) 8 have shown severe cerebral manifestations or signs or symptoms of failure of the heart or of the kidneys. Almost all (96 per cent) have symptoms, which are often severe, headache being especially prominent.

CASE 5 (table 4)—D. B., a 22 year old stenographer, had scarlet fever at the age of 7 years and diphtheria a year later. Her father died at the age of 54 of heart disease, when she was 20. She was perfectly well until his death, which was a great shock to her and from which she dated her symptoms. She began to tire easily and became excessively nervous. She lost no weight.

The basal metabolic rate was +34 and +37 per cent. The pulse rate was elevated. The rate of phenolsulfonphthalein excretion was 60 per cent in two hours. The systolic pressure was 190 and the diastolic pressure 150. Iodine medication was prescribed, but the basal metabolic rate remained high (+48 per cent) and the pulse rate rapid (125). Severe occipital headaches began, which were often incapacitating. One year later she noticed dyspnea on exertion, occasional attacks orthopnea and swelling of the ankles. The systolic pressure rose to 210 and the diastolic pressure to 150. Dyspnea became rapidly worse. She was admitted to this hospital, Dec. 16, 1933.

24 Huchard, H. *Traite clinique des maladies du cœur et de l'aorte*, ed. 3, Paris, O. Doin, 1899, vol. 1, p. 74.

25 Herrick, W. W. *Hypertension and Hyperglycemia*, J. A. M. A. **81** 1942 (Dec. 8) 1923.

The patient was slightly orthopneic. The ocular fundi showed slight papilledema. The arteries were constricted almost to obliteration, with marked peri-vasculitis, there were a few small hemorrhages and large patches of white exudate. The thyroid gland was not enlarged, and there was no tremor of the hands. Von Graefe's sign was not present. There was congestion at the bases of both lungs. The heart was enlarged and markedly overactive, and there was gallop rhythm. The systolic pressure was 220 and the diastolic 180. There was no edema. The urea clearance was 43 per cent of normal. The maximal specific gravity of the urine was 1.015. There were moderate albuminuria and microscopic hematuria. The systolic pressure during two weeks varied from 228 to 250 and the diastolic from 188 to 150. The pulse rate remained between 100 and 140. A sudden cerebral accident terminated the illness. At autopsy there were cerebral hemorrhage, early arteriolar sclerotic nephritis, arteriolar sclerosis, hypertrophy of the heart and diffuse basophilism of the pituitary gland.

Summary—This patient had a "malignant" form of arterial hypertension, death from a cerebral accident taking place two years after the onset. Although the basal metabolic rate was elevated, the usual signs of hyperthyroidism were lacking. The diastolic pressure was exceptionally high. The pituitary gland on microscopic examination showed an abnormality.

CASE 21 (table 4)—M. F., a 60 year old housewife, had scarlet fever and diphtheria at an early age. Her mother died of apoplexy at 80. There was no definite family history of hypertension. Of her 4 children, 2 were premature. She was in excellent health until the age of 44, when symptoms of menopause appeared. Coincidentally she noticed severe occipital headaches, and high blood pressure was discovered. As the menopause became established the headaches became worse, but they were never incapacitating.

At 49 she was moderately obese. The heart was normal on roentgen examination, the peripheral vessels were normal, the systolic pressure was 245 and the diastolic 150. The urine was normal. The vessels of the ocular fundi were slightly tortuous. The urea index of Van Slyke was normal. The patient excreted 74 per cent of phenolsulfonphthalein in two hours. The maximal specific gravity of the urine was 1.030. The systolic pressure varied during six weeks' observation from 270 to 200 and the diastolic pressure from 170 to 130. During the next seven years the headaches continued with lessened severity. Other changes were noticed. There was a gradual decline in the blood pressure (which at the time of writing is usually between 220 and 180 systolic and 120 and 110 diastolic), a fall in the clearance of urea from 93 per cent of normal at the age of 53 to 65 per cent at the age of 56, with a decrease in the maximal specific gravity of the urine to 1.025, some increase in the tortuosity of the vessels of the ocular fundi and a slight increase in the size of the heart. During the past three years she has been free from symptoms.

Summary—Arterial hypertension, beginning with the menopause, is now of sixteen years' duration. There has been a progressive decrease both in the blood pressure and in the symptoms.

IV VASCULAR DISEASE

Generalized arteriosclerosis and "essential" hypertension are often found in association. The frequency with which these two conditions occur together suggests that there is some intimate relation between

them, but the nature of this relation is not clear. Although Lange²⁶ concluded that arteriosclerosis may result from hypertension, he admitted that the arterial changes typical of hypertension are confined to hypertrophy of the media. It is known, however, that arteriosclerosis does not always accompany the long-standing hypertension associated with coarctation of the aorta, and it seems uncertain that hypertension alone produces true arteriosclerosis.

Severe generalized arteriosclerosis often occurs without elevation of the diastolic pressure—that is, without arterial hypertension—although the systolic pressure may be elevated, probably owing to a loss of arterial elasticity. The only situation in which hypertension has been believed to result from arteriosclerosis is one in which the renal arteries or their mouths are narrowed by sclerotic changes.²⁷

The commonest form of “essential” hypertension, that observed in older persons, is so often associated with generalized arteriosclerosis that it seems desirable to form a separate group of cases on this basis alone. The usual benign course, ending in heart failure or, more commonly, in a cerebral accident, the absence of symptoms (such as palpitation or headache) and the lack of retinal exudation supply reasons on clinical grounds for regarding such cases as a separate group. In 36 patients (28 men and 8 women) generalized arteriosclerosis was found without other phenomena significant enough to permit placing their cases in one of the other groups.

Twenty of these patients died—9 of a cerebral accident, 2 of cardiac failure, 3 of renal failure and 3 of other diseases. The manner in which the remaining 3 died is unknown. In 2 of those who died in uremia the renal arteries at autopsy were markedly narrowed by sclerotic changes.

The onset of hypertension in 6 (of 36 patients) occurred after the age of 60, in 11 between 50 and 60, in 10 between 40 and 50 and in 7 between 35 and 40. At the time of this report severe symptoms are present in 5 (of 15) living patients. Three have been stricken with cerebral accidents. Severe headaches and palpitation are unusual.

One case of hypertension associated with Buerger's disease and 1 of hypertension associated with lead poisoning are included in this group.

CASE 5 (table 5)—J. K. was a retired barber 72 years old. His mother had died at 78 of “hardening of the arteries.” Two brothers died of tuberculosis. The patient suffered an attack of diphtheria at the age of 10 years. At 30 he contracted a chancre, which was treated with mercury bichloride given by mouth. The Wassermann reaction was negative on many occasions. At 38 the patient was found to have pulmonary tuberculosis and was treated for two years in a sanatorium. Roentgen examinations disclosed some pulmonary fibrosis but no evidence

²⁶ Lange, F., in Cowdry, E. V. *Arteriosclerosis*, New York, The Macmillan Company, 1933, chap. 18.

²⁷ Goldblatt, H. Personal communication to the authors.

TABLE 5—Vascular Disease ##

Case No.	Sex	Patient	Family History	Age at Onset, Years	Duration, Years	Symptoms When First Seen	Average Extremities of Blood Pressure, Mm Hg		Ocular Fundi**		Progress††	Present Status§§	Other Classifications#	Comment
							Highest	Lowest	Marked Generalized Arteriosclerosis	Arterio sclerosis	Hemor rhage or Lxudate			
1	♂	D M	0	<70	>12	0	230/120	180/100	+	+	0	D	0	Died of pneumonia
2	♂	J K	0	<62	>12	0	270/ ?	180/ 90	+	+	0	D R	0	Died of pneumonia
3	♂	J L	0	<61	>12	0	205/115	180/ 95	+	+	0	L	0	Calcification of vessels §§
4	♂	O E	+	61	20	0	175/100	155/ 85	+	+	0	L	0	Calcification of vessels §§
5	♂	J K	+	52	9	0	230/130	210/120	+	+	0	D Ce	0	Calcification of vessels §§
6	♂	J S	+	50	9	0	230/130	200/110	+	+	0	D Ce	0	Calcification of vessels §§
7	♂	A P	0	47	2	0	230/110	200/120	+	+	0	D	0	Calcification of vessels §§
8	♂	M H	0	<39	>2	0	230/150	220/130	+	+	0	D	0	Calcification of vessels §§
9	♂	C L	0	33	8	II C	270/150	210/110	+	+	+	D C R	0	Calcification of vessels §§
10	♂	C S	0	<31	>1	II	270/150	210/110	+	+	+	D R	0	Gastric hemorrhage
11	♀	L H	0	62	10	II C	180/110	170/ 90	+	+	0	D R	0	Marked arteriosclerotic obstruc
12	♀	A W	+	<58	>10	II C	210/105	170/ 95	+	+	0	D C	0	Marked arteriosclerotic obstruc
13	♀	A W	+	51	4	Ce	100/140	160/110	+	+	0	D C	0	Marked arteriosclerotic obstruc
14	♀	II K	+	50	4	Ce	260/160	230/130	+	+	0	D Ce	0	Marked arteriosclerotic obstruc
15	♂	W L	0	53	13	II	210/130	180/110	+	+	0	L	0	Calcification of vessels, §§ diabetes
16	♂	F L	+	<56	>10	Ce	190/110	155/125	+	+	0	D	0	Obesity
17	♂	B B	+	53	3	II Ce	230/130	140/ 90	+	+	0	D ?	0	Arterial fibrillation
18	♂	G L	0	52	7	H C	200/115	155/ 95	+	+	0	I	0	Calcification of vessels, §§ diabetes
19	♂	II W	0	50	7	Ce	230/130	190/125	+	+	0	I	0	Obesity
20	♂	S R	+	<47	>8	Ce	200/115	150/ 95	+	+	0	D Ce	0	Arterial fibrillation
21	♂	G C	0	45	7	0	210/115	150/ 95	+	+	0	L	0	Calcification of vessels, §§ diabetes
22	♂	R L	0	43	7	Ce	210/130	180/110	+	+	0	I	0	Obesity
23	♂	W G	+	43	10	II	240/140	185/110	+	+	0	D Ce	0	Arterial fibrillation
24	♂	J R	+	38	7	II	230/130	200/120	+	+	0	L	0	Calcification of vessels, §§ diabetes
25	♂	J G	+	36	7	II	170/110	150/ 95	+	+	0	L	0	Obesity
26	♂	H M	+	<38	4	0	230/130	200/120	+	+	0	L	0	Arterial fibrillation
27	♂	J L	0	36	4	II	230/130	215/110	+	+	0	L	0	Calcification of vessels, §§ diabetes
28	♂	A K	0	36	6	C	260/160	180/120	+	+	0	L	0	Obesity
29	♂	O T	0	36	4	0	220/150	180/120	+	+	0	L	0	Arterial fibrillation
30	♂	H M	0	36	4	0	210/130	180/110	+	+	0	L	0	Calcification of vessels, §§ diabetes
31	♂	E B	0	36	4	II	170/ 95	150/ 85	+	+	0	L	0	Obesity
32	♂	J S	+	<44	>2	0	240/120	190/110	+	+	0	L	0	Arterial fibrillation
33	♂	J S	+	36	4	0	185/120	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
34	♂	J S	+	36	4	0	215/145	180/120	+	+	0	L	0	Obesity
35	♂	J S	+	36	4	0	235/140	180/120	+	+	0	L	0	Arterial fibrillation
36	♂	J S	+	36	4	0	225/135	183/ 97	+	+	0	L	0	Calcification of vessels, §§ diabetes
37	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
38	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
39	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
40	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
41	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
42	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
43	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
44	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
45	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
46	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
47	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
48	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
49	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
50	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
51	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
52	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
53	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
54	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
55	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
56	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
57	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
58	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
59	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
60	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
61	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
62	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
63	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
64	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
65	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
66	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
67	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
68	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
69	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
70	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
71	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
72	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
73	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
74	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
75	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
76	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
77	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
78	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
79	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
80	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
81	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
82	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
83	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
84	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
85	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
86	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
87	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
88	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
89	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
90	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
91	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
92	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation
93	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Calcification of vessels, §§ diabetes
94	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Obesity
95	♂	J S	+	36	4	0	183/ 97	155/100	+	+	0	L	0	Arterial fibrillation

For explanation of symbols and abbreviations, see footnotes to table 2
 §§ In roentgenograms of the extremities

of active tuberculosis. He was well until the age of 52, when hypertension was discovered. The systolic blood pressure was said to be 170 to 180, and albumin and casts were found in the urine. The blood pressure remained fairly constant until the age of 58, when it began to increase. At the age of 65 the systolic pressure taken on admission to this hospital had reached 230 and the diastolic pressure 130. The only symptoms were slight headache, coming on with excitement, and a moderate amount of dyspnea on exertion, which had been slowly progressing since the age of 61. The patient had three rather profuse epistaxes at 62.

The important physical findings in 1932, at the age of 65 years, were moderate obesity, marked generalized arteriosclerosis with tortuosity and beading of the larger arteries, moderate pulmonary emphysema and slight enlargement of the prostate. Roentgen examination showed the heart enlarged and the ascending aorta moderately dilated. Calcification in the vessels of the extremities was seen in the roentgenograms. In the six years preceding this report the urea clearance has progressively decreased from 73 to 43 per cent of normal and the maximal concentration of the urine to a specific gravity of 1.021. The retinal arteries are moderately tortuous and thickened, there is constriction of the veins at arteriovenous crossings. The systolic pressure has varied from 230 to 200 and the diastolic pressure from 160 to 120. In November 1937 the patient suffered hemiplegia on the right side, from which he slowly recovered. At present he complains of dyspnea on climbing three flights of stairs, occasional dizzy spells, nocturia and an occasional nosebleed.

Summary—In this patient arterial hypertension has persisted for twenty years, associated with marked general arteriosclerosis with evidence of only minimal damage to the heart, vessels and kidneys. He complains of few symptoms. The progress of the ailment has been slow.

CASE 26 (table 5)—W. G., 68 years old, an artist, was known to have had hypertension at the age of 40. His parents died of unknown causes. As a young adult, he contracted gonorrhea, malaria and acute appendicitis. At the age of 54 he had an attack of pneumonia, and two years later he had jaundice with biliary colic, which was relieved without operation. At the age of 40 the systolic pressure was said to be 180. There was some cardiac irregularity, which soon disappeared. Hypertension continued, but he had no symptoms from it until the age of 56, when he noticed that he was obliged to limit his activities. Not until the age of 62 did he complain of mild occipital headaches, slight dizziness and a sensation of transient numbness in the left arm.

At this time (in 1932) he was moderately obese. The systolic pressure varied during three weeks' rest in bed between 230 and 180 and the diastolic between 116 and 100. In the ocular fundi there was moderate beginning arteriosclerosis. The heart was moderately enlarged on roentgen examination. There was some tortuosity of the aorta. A soft systolic murmur was heard at the base of the heart. The peripheral arteries were moderately thickened and slightly tortuous. The urea clearance was 75 per cent of normal. One year later the patient began to complain of nervousness and of some increase in the number of headaches. He was able to continue his work, however, and to live an approximately normal life. Hypertension persisted. At 68 the systolic blood pressure had risen to 230 and the diastolic pressure to 130. This was accompanied by an increase in the size of the heart. The urea clearance was 85 per cent of normal, and there was slight proteinuria. The patient was well except for headaches until the day he died, suddenly, of apoplexy at the age of 68.

Summary—This was a case of long-standing arterial hypertension associated with arteriosclerosis. There were few symptoms. A cerebral accident was the terminal event.

V UNCLASSIFIED

There were 37 cases which could not be readily classified according to the scheme adopted in this study. In 10 the facts known were insufficient for a proper diagnosis. Of the remaining 27, although considerable information was available, data which we have come to regard as essential for purposes of this classification were lacking in all but 6. The onset of hypertension occurred in 4 (of these 27 cases) during pregnancy. In 6 hypertension was very mild. Three belonged possibly in group II and 3 in group III. In 5 rapid progress of the "malignant" type marked the course. In 1 case marked emotional instability was exhibited. In the remainder (5) there were no characteristic phenomena by which classification could be attempted.

CASE 4 (table 6)—M. R., a 36 year old housewife, had always enjoyed excellent health until the birth of her fourth baby. There was no history of hypertension in the family. At the age of 21 she was said to suffer from malaria. She had always been nervous and high strung and usually underweight. The first three pregnancies, at the ages of 22, 25 and 27, were normal, no rise in the blood pressure was noticed. At the age of 29, during the fourth pregnancy, the blood pressure became elevated during the seventh month, reaching a level of 228 systolic and 138 diastolic. The patient complained of no symptoms at this time, and delivery was normal. The urine was normal until delivery, but during the first two weeks post partum there were marked albuminuria and pyuria, both of which disappeared before her discharge from the hospital. Hypertension persisted, however, exhibiting the following course. At the age of 31 the systolic pressure was 260 and the diastolic 140, and at 33 the systolic pressure was 290 and the diastolic 160. At the age of 34 she had hemiplegia and became totally blind. The systolic pressure was 230 and the diastolic pressure 130. Although the paralysis gradually disappeared, she never recovered her sight. Severe headaches, from which she had suffered a few months before this, disappeared only to recur two years later. She was admitted to this hospital with headache as her only complaint.

Important physical findings were a systolic pressure of 300 and a diastolic pressure of 165, almost total blindness, some increase in the deep reflexes on the right side, with a possible Babinski reaction, slight thickening of the peripheral vessels, moderate enlargement of the liver and duplication of the first sound of the heart. In the ocular fundi there were papilledema, well marked perivascularitis, evidence of old and fresh hemorrhages and marked atrophy of the optic nerves. The urea clearance was 55 per cent of normal. The maximal specific gravity of the urine was 1.017. The systolic pressure varied between 300 and 180 and the diastolic between 165 and 110, falling slowly after therapy with sodium thiocyanate but rising to 242 systolic and 138 diastolic when this treatment was discontinued. Shortly after this, coma set in, from which she did not recover. She died at the age of 38. At autopsy there were observed cerebral hemorrhage, generalized arteriolosclerosis and arteriolosclerotic nephritis. The kidneys showed many local scars, thickly infiltrated with lymphocytes.

Summary—Hypertension began during the seventh month of the fourth pregnancy, cerebral symptoms predominating. It is uncertain whether infection of the kidneys or some endocrine disturbance was present at the onset, although the former seems more likely. Classification could not be attempted without more knowledge of what was abnormal during pregnancy.

TABLE 6—Unclassified Hypertension ##

Case No	Sex	Patient History	Family History	Age at Onset, Years	Duration, Years	Symptoms When First Seen	Average Extremes of Blood Pressure, Mm Hg		Ocular Fundi**		Progress†	Present Status§	Other Classifying Signs#	Comment
							Highest	Lowest	Arterio sclerosis	Hemorrhage or Exudate				
1	♀	B A	+	23	4	H	240/160	180/120	+	++	R	D R	0	Emotional instability
2	♀	M P	0	22	8	0	180/135	150/110	0	0	0	L	0	
3	♀	D L†	0	19	6	H	270/180	170/110	+	++	R	D R	0	Obesity
4	♀	M R	0	29	7	H Ce	260/160	220/120	+	+	Ce	D Ce	0	
5	♂	J A†	0	37	5	H C	240/160	180/130	0	0	C Ce	D C	0	
6	♂	P M†	0	36	2	H	270/170	190/130	++	+	Ce	D Ce	II+IV+++	
7	♂	P M†	0	<39	>2	H C Ce	260/170	210/110	+	0	Ce	D Ce	IV++	
8	♂	I G	0	44	6	H C	260/150	180/120	0	+	C	D C	II++	
9	♂	M P	0	31	4	H C	270/180	210/140	+	+++	C R	D C R	II+IV+++	
Possibly Belonging to Groups														
10	♂	J R	0	31	12	H	170/110	140/95	±	0	0	L	II+++	Possibly diencephalic
11	♀	E J	0	18	2	H	210/130	155/100	0	0	0	L	II+++	Possibly diencephalic, congenital heart disease, marked lumbar scoliosis
12	♀	M A	0	19	2	0	210/140	105/130	0	+	0	L	II++	Possibly diencephalic, emotional instability
13	♀	J S	0	35	11	0	240/130	210/115	+	0	Ce	D Ce	III++	Obesity
14	♂	F G	+	10	10	0	200/100	170/80	0	0	0	L	III++	Treated for pituitary dyscrasia at 12
15	♂	M M	0	<41	>9	0	180/115	160/105	±	0	0	L	III++	Marked obesity
Miscellaneous														
16	♀	R P	0	16	3	0	160/90	110/70	0	0	0	L	II++II+	Mild hypertension, obesity
17	♂	G S	0	17	3	0	150/95	135/80	0	0	0	L	II++	Mild hypertension
18	♂	M F	0	28	8	H	170/110	110/80	0	0	0	L	0	Mild hypertension
19	♂	B P	0	19	6	H	145/95	135/80	0	0	0	L	III+	Mild hypertension
20	♂	A L	0	17	2	0	170/100	135/80	0	0	0	L	II++	Mild hypertension
21	♂	P H	0	19	2	0	160/90	135/80	0	0	0	L	II++	Mild hypertension
22	♀	R R	+	27	3	H	210/115	140/90	0	0	0	L	II+	Mild hypertension
23	♀	M M	+	36	7	Ce	260/115	200/120	0	+	0	L	II+	Emotional instability
24	♀	B G	0	24	2	0	270/170	220/150	0	+	0	L	0	Unclassifiable
25	♀	J K	0	20	18	H C	200/135	190/130	+	+	C	D Ce	II++IV+	Unclassifiable
26	♀	M A	+	20	11	H	210/130	190/120	±	0	0	L	0	Unclassifiable
27	♀	F C	+	25	2	0	210/130	180/120	0	0	0	L	0	Unclassifiable
Insufficient Data														
28	♀	N W	0	52	?	H	220/120	210/100	?	?	?	D	IV+++	Moderate arteriosclerosis
29	♂	H L	0	<56	?	C	210/110	180/110	?	?	C	?	0	
30	♂	A M	0	50	?	C	200/110	180/100	?	?	?	?	IV+	
31	♂	E J	0	48	?	H	240/160	200/140	+	+	?	?	IV+	
32	♂	E W	+	29	1	0	250/150	200/130	+	+	C R	D C R	IV+	
33	♂	A O	0	39	>7	H C	240/160	190/120	?	?	?	?	IV++	
34	♂	A M	0	35	>7	H	240/160	190/130	+	+	?	?	III++	Obesity, menorrhagia
35	♂	E V	0	<39	>9	H	230/140	190/130	+	+	Ce	D	IV++	
36	♂	M D	+	<27	>2	H C	200/140	180/125	0	0	Ce	D Ce	III+	
37	♂	L S	0	49	>5	H	240/140	185/110	+	0	?	?	II++	
			19%+	Average 30.4 yr	Average 5.6 yr	50% H >20% O	Average 217/131	Average 178/111	33%+	42%+	45% D (33% with renal failure)			

For explanation of symbols and abbreviations, see footnotes to table 2

COMMENT

Although "essential" hypertension has been regarded as a primary disease for a number of years, the question is raised again whether it is not merely a syndrome common to a number of maladies. If so, some or all of the contributing mechanisms would be better understood if viewed in association with coexistent disturbances. The adoption of this attitude has been useful in understanding and in classifying cases in which hypertension has been considered "essential" and in which the underlying abnormal processes have been unsuspected. The fact that these abnormal processes appear to be chiefly related to the four systems set forth in the classification simplifies the problem of discussion. Comments are made under the four main headings.

I When renal failure is present, it is of course known that arterial hypertension may accompany many diseases of the kidneys. When in the absence of renal insufficiency arterial hypertension is associated with organic renal disease, it is naturally not known what part the renal lesion has played in bringing it about. Renal disease can be regarded as causally related to hypertension only in cases in which the diastolic pressure has fallen after removal of a diseased kidney.

Certain renal abnormalities seem, therefore, to occasion hypertension, although they occur also in its absence. Those now reported in cases in which hypertension has been considered "essential" cannot be shown conclusively to have caused it. However, the frequency with which renal abnormalities are found in such cases and the fact that their presence often antedates the elevation of blood pressure suggest that they bear some intimate relation to that elevation. In all events, the patients in this group are indistinguishable from those who have been regarded as suffering from "essential" hypertension except that 61 per cent of them have sustained some damage to their kidneys before the development of hypertension and the remainder exhibit signs of renal disease without failure, the nature of which is not usually believed to be associated with elevated arterial pressure. The condition is now designated "renal hypertension without failure."

The observations that a rapid course is not unusual (35 per cent), that hemorrhagic and exudative lesions of the retina are common (65 per cent) and that death from renal failure is often the outcome (76 per cent) suggest that cases of this type form a distinct group.

II A different group is that in which arterial hypertension is exhibited along with the "hypertensive diencephalic syndrome." Although the evidence, experimental and clinical,²⁸ that the diencephalon is

28 Bard, P. The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, *Arch Neurol & Psychiat* 22 230 (Aug) 1929

involved is indirect,¹⁶ there is a preponderance of symptoms suggesting derangement of certain functions of the nervous system. There is further evidence indicating that these cases form a separate group. The arterial hypertension is benign. It occurs in younger persons and occasions few of the signs commonly associated with hypertension at this age. Changes in the retina, cardiac enlargement and failure of renal function are unusual. The marked lability of the blood pressure is noteworthy, even if hypertension has been present for many years. The progress of the disease appears to be extremely slow even when the blood pressure is markedly elevated. Patients on whom section of the anterior spinal nerve roots has been performed have improved,²⁹ though the meaning of this improvement is not clear. On clinical grounds, therefore, this group appears to constitute a special variety of cases of "essential" hypertension. Because of the predominance of symptoms depending on disturbances of the nervous system, the hypertension is designated "nervous hypertension."

III Although disturbances of the endocrine glands have sometimes been believed to be associated with "essential" hypertension, it is still not clear whether dysfunction of these organs can be responsible for elevation of arterial pressure except in cases of pronounced endocrine dyscrasia (e. g., cases of Cushing's syndrome). However, endocrine dysfunction of less pronounced form is undoubtedly associated with "essential" hypertension in some cases, being present in 19 per cent of ours and in many instances (51 per cent) appearing at the onset of the disease. We have called such a condition "endocrine hypertension."

The cases in this category exhibit clinical differences, although the complaint of severe headache is frequent. In cases of "nongoitrous thyrotoxic hypertension" the illness progresses rapidly, symptoms are severe, and hemorrhagic and exudative lesions are seen in the retina. In cases in which hypertension begins at the menopause it runs a benign course. The same is true in cases in which hypertension follows recovery from hyperthyroidism. While in 10 of 43 patients the course was consistent with the diagnosis of malignant hypertension, 13 have lived more than ten years.

IV Arterial hypertension is now believed to follow lesions of the blood vessels only when these lesions involve the arteries supplying the kidney. In animals, elevation of the diastolic pressure can be produced by partial constriction of these arteries. In human beings a similar mechanism is believed to be operative when they are narrowed by arterio-

29 (a) Page, I. H. Medical Aspects of Surgical Treatment of Hypertension, *J. A. M. A.* **110** 1161 (April 9) 1938. (b) Page, I. H., and Heuer, G. J. Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots, *Arch. Int. Med.* **59** 245 (Feb.) 1937.

sclerosis (Goldblatt,²⁷ Leiter¹⁰) Hypertension occurring with periarteritis nodosa of the renal arteries and that occurring with coarctation of the aorta may depend on a similar defect Whether narrowing of the *intrarenal* arteries by degenerative changes plays a part in the genesis of hypertension is still uncertain, although such changes are frequently seen in elderly persons

Older patients with general arteriosclerosis and high diastolic pressure exhibit enough clinical uniformity for their cases to be regarded as belonging to a separate group The justification for this suggestion consists of a lack of certain signs (such as exudative lesions in the retina) and symptoms (such as headache or palpitation) common in other cases and of the absence of renal lesions, of disturbances of the nervous system and of endocrine dysfunction In addition, the course is usually benign (87 per cent), arteriosclerosis of the vessels of the retina (but not retinitis) is common (97 per cent), the terminal event is often apoplexy (64 per cent) We designate the hypertension shown in this group "arteriosclerotic hypertension"

No distinction has been made between so-called benign and malignant hypertension It has been found impossible to place cases in which the course is rapidly downhill in a separate group, since most of them exhibit the same phenomena used in classifying cases in which the course is "benign" Further studies are necessary to learn whether these cases form a separate group

This study suggests that "essential" hypertension is not a primary disease The fact that this diagnosis is made by exclusion should indicate multiple causes *The differences found among groups of cases is evidence that many causes are possible In too many instances the associated disturbances may be significant The unity of "essential" hypertension is, therefore, seriously called into question In the light of this recital the need for a new classification is obvious The present classification cannot be regarded as more than tentative It has already been of advantage in facilitating diagnosis, in making prognosis more accurate and in setting the indications for therapy on a more reasonable basis It is desirable that other means of differentiation be utilized to establish what is "essential" in this condition

SUMMARY

Two hundred and eighteen cases of so-called "essential" hypertension have been studied and classified from the standpoint of the varied phenomena which have been observed Five main groups have been tentatively distinguished on the basis of the criteria used (1) renal, (2) nervous, (3) endocrine, (4) vascular, and (5) unclassified These groups exhibit disorders in the same systems as do those in which secondary arterial hypertension is found

SHOCK

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The physician confronted with a gravely ill patient, pallid and cyanotic, with a rapid, hardly palpable pulse and frequent, shallow breathing, thinks of heart failure and injects digitalis. This procedure, however, is the right one in only part of the cases, for frequently the condition described has nothing to do with poor heart action. I must admit that I have made this mistake myself on several occasions. I have needed much time to realize how little is generally achieved by stimulation.

One must always consider whether the heart has caused this serious condition or whether the picture should be ascribed to peripheral circulatory failure. In the latter case one speaks of the shock syndrome. A precise knowledge of the symptoms will always enable the physician to differentiate the two conditions.

In medical literature and especially in common parlance there is much confusion about shock. Though I have chosen to term the clinical syndrome underlying peripheral circulatory failure shock, because this term is in general use with investigators in this field, others prefer to speak of collapse. Still others use both terms indiscriminately. Tendeloo differentiated between collapse, on the one hand, and psychic or traumatic shock on the other. Since, however, it can be demonstrated that both conditions have the same pathogenesis, it is erroneous to use these names as if they designated different conditions.

For a long time shock was known to the surgeon only as an effect of injury or operation. Romberg and Paezler were the first to introduce the concept of shock into the literature of internal medicine. They emphasized that the deterioration of the pulse in acute infectious diseases is generally a result not of heart failure but of peripheral circulatory weakness caused by vasomotor paralysis. During and after the great war much work was done on the pathogenesis of traumatic shock, and only then was it realized how frequently this syndrome occurs in all kinds of internal diseases. By shock I mean the clinical syndrome resulting from a discrepancy between the blood volume and the capacity of the vascular system¹. All considerations on the subject must be regarded from this point of view.

¹ Moon, V H. *Ann Int Med* 8 1633, 1935. Freeman, N E, Shaw, J L, and Snyder, J C. *J Clin Investigation* 15 651, 1936.

Under these circumstances the large veins are poorly filled, the heart receives too little blood, and the cardiac output becomes less. Accelerated heart action ensues in an attempt at compensation, but if the minute volume nevertheless decreases, a marked fall of the blood pressure is inevitable.

The considerable fall in blood pressure, the poorly filled large veins and the small heart figure are the principal landmarks that distinguish peripheral circulatory failure from heart failure. In the latter condition an important decrease of the blood pressure is rarely met with, and the dilated heart and engorged veins clearly point to a different condition.

SYMPTOMS OF THE SHOCK SYNDROME²

The skin is pale. The lips, ears and nails are cyanotic. The body is cold and clammy, especially the nose, fingers and toes. Sometimes the skin is dry and its elasticity low, sometimes it is covered with drops of sweat, depending on the cause of the shock. *Cutis marmorata* is a sign of poor circulation and results from irregular filling of the subpapillary venous plexus. The rectal temperature is often lowered, but there may be pyrexia in spite of the coldness of the skin.

The patients prefer lying flat in bed, in contrast to patients with cardiac disease, most of whom suffer from orthopnea. The cheeks are sunken, the eyes lie deep. The description corresponds to *facies hippocratica*, in fact, in peritonitis the shock syndrome is often outstanding.

Consciousness is variously influenced. Some of the patients are apathetic, do not reply to questions and hardly react to stimuli. Therefore, these patients do not complain of the violent pain that may have caused the shock (coronary occlusion, injury). Others, however, are conscious to the very end, replying to questions in a hardly audible voice but correctly. Still others are restless and exalted and want to leave their beds.

I recently saw a patient in profound shock due to gastric hemorrhage. He was unreasonable, he screamed and could be kept under control only with much difficulty during the blood transfusion, which was carried out with all speed. During the transfusion the pulse improved, the skin became warm, and the restlessness disappeared. Bleeding patients who become restless in this way require the utmost care. They may be in shock, and when given morphine they may die unnoticed. The patients complain of thirst. When given a drink, they vomit, the vomitus being often mixed with blood. During the shock of diabetic coma I have repeatedly seen the typical brown vomitus of hemorrhage by diapedesis.

² Fishberg, A. M. *Heart Failure*, Philadelphia, Lea & Febiger, 1937.

Respiration is usually shallow and rapid with occasional deep sighing. On a few occasions I have observed Cheyne-Stokes and Kussmaul respiration.

The pulse is rapid and soft. Often its rate increases, sometimes to 160 or 180. Not infrequently the pulse is impalpable.

The blood pressure is generally much decreased. This applies to both the maximal and the minimal pressure. Sometimes the blood pressure can be measured only by palpation. The maximal value (systolic) is often below 70 mm. of mercury. The tachycardia is probably a response to the low aortic pressure. When one succeeds in bringing the blood pressure to a suitable level by infusion, one finds that the pulse rate falls almost simultaneously. At the onset of shock the blood pressure is sometimes temporarily raised, the compensatory contraction of the arteries as a result of the lowering of blood volume may be intense. (This rapid and marked fall of the blood pressure is never found in heart failure. In that condition the blood pressure is in general normal or raised, and not before the agonal stage is it seen to decrease.)

The heart can be delimited by percussion with difficulty. When under these conditions a roentgenogram is taken, the heart is found to be very small. The cardiac sounds are soft, the second sound because of the low blood pressure, the first because the muscular sound is weak, owing to the low cardiac output. Thus a sensation of embryocardia can be obtained.

The superficial veins are collapsed, which becomes obvious on attempts at venipuncture. The pressure in the vein may even be below 1 to 2 cm. of water.

The reflexes are low. The pupils are dilated and react defectively to light.

The urinary output is generally low. Occasionally I have seen anuria develop. The specific gravity of the urine, in contrast to that in cases of circulatory congestion is usually low. Sometimes typical isosthenuria is observed. The poor renal function, as well as extra-renal factors, leads to uremia. Renal failure must be ascribed to the lessened flow of blood through the kidneys, with anoxemia supervening. The kidneys are severely damaged, since their function requires much oxygen. This is comparable with the renal insufficiency of severe anemia.

Diuresis is much lowered when shock is attended by dehydration due to vomiting and diarrhea. The extra-renal factors causing uremia are dehydration, fever and autolysis. The blood often shows a loss of chlorides and bases (sodium). Generally there is acidosis. I have often found values for alkali reserve between 20 and 30 volumes per cent. The causes of acidosis are manifold. Owing to the anoxemia,

intermediary metabolites are incompletely oxidated. The resynthesis from lactic acid is decreased, which causes the lactic acid content to rise. At venipuncture the dark color of the blood is always conspicuous. On analysis the oxygen content is found to be below normal. This is due to the fact that the slow blood stream gives off much of its oxygen. Yet the tissues receive too little oxygen.

The temperature is lowered as the production of heat becomes defective through slowing of the blood stream, and the fall in temperature is enhanced by the accelerated breathing and sweating. On account of its slow current the blood cools excessively.

I have repeatedly emphasized that the heart is not the cause of this condition. The heart in failure is always dilated, except in paroxysmal tachycardia and concretio cordis. Another circumstance which shows the heart to be healthy in shock is that when one replenishes the decreased blood volume by infusion one often has to use several liters of fluid before the blood pressure is reestablished. It is found that the heart can stand this extra burden without damage. I do not think one can load the circulation with so much fluid with impunity if the heart is diseased. At autopsy, however, the heart is often observed to be flabby and dilated. This observation has checked the development of knowledge of shock for a long time. During life the heart is found on roentgen examination to be small. Probably it is dilated shortly before death, when it succumbs to the damage caused by poor circulation.

It is remarkable that a number of quite different diseases can all lead to the identical, sharply outlined syndrome of shock. Among the causative factors may be mentioned hemorrhage, acute infective diseases, poisoning, injury, pain, emotion, operations, loss of fluid by vomiting and diarrhea, perforation of abdominal viscera, pancreatitis, peritonitis, pulmonary edema, coronary thrombosis, pulmonary embolism, burns, congelation, hyperthermia, anaphylaxis, diabetic coma and Addison's disease.

PATHOGENESIS³

All these conditions must have one factor in common, which leads to the shock syndrome. This common factor is the discrepancy occurring in all these conditions between the blood volume and the capacity of the vascular system. This discrepancy may occur in any of three ways:

- 1 By a decrease of the blood volume
- 2 By an increase of the vascular capacity
- 3 By a combination of these factors

A decrease of blood volume in its simplest form is caused by serious loss of blood, of the kind most commonly observed in cases of bleeding.

³ Wiggers, C. J. *Physiology in Health and Disease*, ed. 2, Philadelphia, W. B. Saunders Company, 1937.

peptic ulcer The shock caused by such a decrease is by far the easiest to understand and is most simply mended by blood transfusion A decrease of blood volume may also be the result of dehydration The loss of fluid may be due to severe vomiting or diarrhea or to intense polyuria, as in diabetes In examination of the blood dehydration manifests itself by a high hemoglobin content, a high red cell count, a high cell volume in the hematocrit and a raised level of plasma protein The concentration of the blood may increase by 20 to 50 per cent

Loss of fluid may be brought about in still another way Cases of shock are frequently observed in which the circulating blood volume is decreased by exudation of plasma Harkins⁴ spoke of "plasma-exudation", Eppinger,⁵ of *seröse Entzündung* When this occurs there is concentration of the corpuscular elements of the blood (hemoglobin content, red cell count and hematocrit value are high), but with a normal level of plasma protein A quantity of plasma must have escaped from the circulatory system Eppinger was able to prove this by demonstrating an increased production of lymph in animals in histamin shock

A Decreased blood volume

- 1 Loss of blood normal blood constituents
- 2 Dehydration high values for protein and hemoglobin
- 3 Loss of plasma high values for hemoglobin and normal values for protein

B Increased vascular capacity

- 1 Central (vasomotor paralysis)
- 2 Peripheral (vascular poisons)

C A and B combined

This is easily understood in cases of peritonitis, pulmonary edema, war gas poisoning, combustion and freezing (Harkins) Blalock⁶ was able to demonstrate that contusion, combustion and freezing of a limb caused a considerable increase in its weight as compared with that of the untreated limb

Shock may be brought about by general damage to the capillaries This is probably the explanation of traumatic shock (Moon) Substances are absorbed from the injured area which damage the capillaries This has been proved experimentally When an extremity of an animal is crushed, no shock follows if the femoral vein is ligated As soon, however, as the ligature is released, symptoms of shock appear Furthermore, aqueous extracts have been derived from the injured tissues which when injected into the blood stream of animals cause shock

4 Harkins, H N Ann Surg **102** 444, 1935 Harkins, H N, and Harmon, P H *ibid* **106** 1070, 1937

5 Eppinger, H, Kaunitz, H, and Popper, H Die seröse Entzündung Eine Permeabilitäts-Pathologie, Berlin, Julius Springer, 1935

6 Harrison, W G, Jr, and Blalock, A Ann Surg **96** 36, 1932

In all such cases high values for hemoglobin are found, with a normal protein content. Probably histamine-like substances are in play, which are known to be formed in destruction of tissue. In fact, the best way of studying shock experimentally is by injection of histamine into animals. Shock can be produced experimentally also by implantation of living or injured tissue in the abdominal cavity.

The post mortem observation in cases of death from traumatic shock completely correspond with the findings in experimental shock, the peripheral veins are empty, the viscera are swollen and deep red and the small venules and capillaries of the viscera are engorged. There is blood-stained exudate in the body cavities. The mucous membranes of the thoracic and abdominal organs are red and swollen. Numerous hemorrhages are observed, and when the course has not been too rapid there is pulmonary edema. Taken together, these observations point to a loss of tone of the smaller vessels and to extravasation of plasma—changes which one knows as effects of vascular poisons. The same picture is observed in patients who have died in shock from acute infective disease, after injections of gold compounds (Heubner), and in poisoning by mercury (McNider), alcohol, ethyl carbamate (urethane) or barbitol. Peptone, albumose, histamine, bacteria or bacterial toxins may also be the cause.

Even in cases of combustion and war gas poisoning, however, there is, in addition to local exudation of plasma, general damage to the capillaries, which causes depletion of the blood volume.

Not only decrease of blood volume but increase of vascular capacity may be the cause of the discrepancy. Under normal conditions only part of the capillaries are patent at the same time. If all the capillaries of the skeletal muscle system opened simultaneously, they could easily contain the whole blood volume (Kioch). Under certain circumstances the capillaries do not respond to the stimuli that should make them contract, thus they withdraw the blood from the circulation just as a sponge absorbs water. In this way the volume of the vascular system is considerably augmented. Dale proved that histamine, among other substances, brings about such vascular atony. It causes the capillaries and venules to become dilated and crammed with blood. With the dilatation there is increase in the permeability of these vessels, resulting in concentration of the blood and edema of the tissues. Part of the blood, therefore, may be stored in the skin (*cutis marmorata*). Blood obtained from the capillaries of the skin by pricking the finger shows a considerably higher red cell count than does blood derived from the cubital vein. It is clear, therefore, that shock in many cases is due to a combination of the two factors mentioned, i. e., decreased blood volume and increased vascular capacity. In the dilated capillaries the blood flows slowly or not at all and is thus withdrawn from the circulation. In determinations of the circulating blood volume by

the congo red method the stain does not mix with this stagnant blood, so that a reduced blood volume is found, and, in fact, this is practically the cause. The patient is said to bleed to death in his own vessels. Whether the blood volume is reduced by hemorrhage, by loss of plasma or by withdrawal of a portion of the blood from the circulation, the result is practically the same.

ASSOCIATION OF SHOCK WITH VARIOUS CONDITIONS

Trauma—During the war shock was seen to develop immediately after injury or after a lapse of hours (up to twenty-four). Ordinarily under these conditions shock was called primary and secondary. It was often observed that the late onset of shock coincided with a long-lasting transport, which added the factor of cold to the agents reducing the volume of circulating blood.

Primary traumatic shock develops suddenly, immediately following physical or mental injury. The sudden onset suggests that the nervous system plays an important part. Primary shock may result also from stimulation of the vagus nerve or from paralysis referable to the sympathetic nerves. Lewis referred mainly to vagal stimulation in his description of vasovagal syncope, in which low blood pressure accompanies slowing of the pulse. This description corresponds with Tendeloo's concept of shock. Abdominal operations may cause a sudden fall of the blood pressure, with slowing of the pulse. This is also ascribed to vagal stimulation. Epinephrine immediately relieves the condition. This type of shock Phemister and Livingstone saw in 17⁷ of 175 gastric operations and in 29 of 209 operations on the gallbladder. With nitrous oxide anesthesia this type of shock is rarely encountered. Primary shock is seen also in cases of perforation of abdominal viscera after an injury to the abdomen or the testicles. This process has been compared to Goltz's experiment, in which vasodilatation of the splanchnic area is brought about by repeated tapping on the abdomen. In this instance also the blood accumulates in the abdominal vessels. Paralysis referable to the sympathetic nerves can also give rise to shock, for instance, paralysis produced by a lesion of the cervical portion of the spine or by spinal anesthesia. In this form of primary shock the circulating blood volume is reduced by stagnation, but the blood is not concentrated. Yet it remains questionable whether this explanation holds for all types of primary shock, as several surgeons have assured me that they have not observed the engorgement of the abdominal vessels which should result. Besides, experiments are on record in which stimulation of the abdominal portion of the vagus nerve led to a rise of the blood pressure. It is a difficult field of investigation, as the patients either recover from primary shock rapidly or die rapidly.

7 Phemister, D. B., and Livingstone, H. *Ann Surg* 100 714, 1934

Secondary shock develops later and in general is much more serious. The aforementioned considerations of Moon make it probable that generalized toxic damage to the capillaries is in play. In this form of shock the reduction in circulating blood volume is constant. The more severe the shock, the greater the reduction. A decrease of 85 per cent has been observed.

For a long time the opinion has prevailed that traumatic shock is caused by vasomotor paralysis. It has, however, been shown repeatedly that the vasomotor system well retains its excitability for carbon dioxide. The pale skin also demonstrates arterial spasm, which is hardly consistent with reduced vasomotor activity. The picture rather suggests that the vasomotor center responds well, for the contraction of the cutaneous vessels may warrant a sufficient blood supply to the brain and heart for a long time.

The probable causes of traumatic shock are generalized dilatation of the visceral capillaries with exudation of plasma and local dilatation with extravasation of blood and plasma in the injured parts.

*Postoperative Conditions*⁸—Shock occurring after surgical intervention is ascribed to the same factors. Histamine-like substances should likewise be released into the blood stream. There are a lowered venous pressure and a reduced blood volume. Handling of the intestines is said to lead to the extravasation of much plasma (Blalock). The factor of dehydration should not be lost sight of, being a factor common to all operations.

"Purging" of the patient, restraint on the fluid intake and loss of water by deep respiration are factors not to be underrated.

Loss of Blood—Shock due to this condition is easiest to explain. Much depends on the quantity of the hemorrhage and the speed of the bleeding. When a patient with gastric hemorrhage succumbs, it is the result of shock. Treatment, therefore, should be directed against shock by refilling the vascular system. In cases of serious involvement I resort not to simple blood transfusion but to intravenous drip infusion, which permits continuous administration of the fluid, the volume being controlled under guidance of the pulse and blood pressure. One may make a choice among various fluids—blood, Bayliss' fluid^{8a} or Ringer's solution. I think that this method represents progress in the treatment of life-endangering hemorrhage. Statistics showing mortality reduced under this treatment do not tell much, the fact that I have succeeded in rescuing patients in deep shock, pulseless and with no measurable blood pressure, is a more valuable testimony.

8 Mann, F. C., and Essex, H. E. The Present Status of the Problem of Traumatic Shock, in *Collected Papers of the Mayo Clinic and the Mayo Foundation*, Philadelphia, W. B. Saunders Company, 1935, vol. 27, p. 1231.

8a Bayliss' fluid consists of 60 gm. of acacia, 9 gm. of sodium chloride and 1,000 gm. of distilled water.

Acute Infectious Diseases—Shock is frequently observed in the course of infections. Except in rheumatic fever and diphtheria, a disturbance of circulation in the course of an infection is generally not caused by the heart. This type of shock has been well investigated by Romberg and Paeszlei. They supposed the cause to be vasodilatation due to vasomotor paralysis. Further investigations by means of animal experiments have shown that the lowered excitability of the vasomotor centers is a result rather than a cause of the shock.

During an epidemic of influenza in 1920 Underhill and Ringer⁹ found shock with marked concentration of the blood (hemoglobin content 140) in the cases in which the outcome was fatal. They compared this condition with what they had seen in cases of phosgene poisoning, noting, however, that in the latter the picture developed in hours, whereas in the cases of influenza days were required. In both types of cases there were pulmonary edema and intense hemoconcentration. The latter sign, however, is far from constantly found in cases of acute infectious diseases in which shock has developed. It is my experience that in most cases it is not present. In January 1937 I had an opportunity of examining closely a number of patients with influenza who died in shock. In spite of a complete and distinct picture of shock, with a blood pressure of 50 to 60 mm, a hardly palpable pulse and empty veins, these conditions generally persisting for several days, I never found a rise in the red cell count or in the cell volume. My experience with shock in patients suffering from other acute infective diseases, particularly in a number of patients with pneumonia and scarlet fever, is of the same kind, there was no concentration of the blood even to the ultimate stage. Recently a man suffering from tropical malaria was admitted to the hospital in deep shock. He died an hour later, and there was no concentration of the blood. I do not know how to explain shock in such cases. The great resemblance to traumatic shock, in which there is certainly a reduced blood volume, makes it probable that in these cases also toxins are in play, acting peripherally on the capillaries and causing dilatation with or without extravasation of plasma. I have never succeeded in saving a patient in severe shock from infectious disease.

Poisoning—In various kinds of poisoning the shock syndrome may be studied. I have observed it in veronal (barbital), mercury bichloride, arsenic and oxalic acid poisoning. In war gas poisoning, especially, shock develops extremely rapidly, and the management of this poisoning is mainly the treatment of shock. A patient who had taken about 13 Gm of arsenic acid was admitted to the hospital five hours later. He was in typical shock. The pulse could not be felt, nor could the blood

⁹ Underhill, F. P., and Ringer, M. Blood Concentration Changes in Influenza, with Suggestions for Treatment, *J. A. M. A.* **75** 1531 (Dec. 4) 1920.

pressure be determined. The erythrocyte count was 7,000,000 per cubic millimeter. An intravenous drip temporarily raised the blood pressure to 80 mm systolic, and the circulation improved. The success, however, was transitory, as the patient died with the signs of pulmonary edema.

Vomiting and Diarrhea—Here the supervening of shock is easily understood when one realizes how much fluid may be lost by the patient. Not only the tissues but the blood is dehydrated. The picture of dehydration and concentration of blood may be striking. Loss of salt and uremia also develop, but these are secondary symptoms. The danger lies in a reduction of the blood volume incompatible with life. In recent years much has been written about "extra renal uremia," caused by dehydration on loss of salt. Yet I do not think that in this case the danger comes from uremia. The menace should be sought rather in the reduction of circulating blood volume. Treatment should be directed to combating dehydration by means of fluid or salt. By these means shock is abolished, and uremia disappears as the circulation improves. This form of shock is amenable to therapeutic intervention. Fluid up to several liters is often required for replenishing the loss, the red cell count being a practical means of estimating the dose. When one realizes that up to 7 liters a day has been given in these conditions, partly intravenously, one understands that good cardiac function must have been present. I observed severe shock in a few cases of paratyphoid fever with severe diarrhea. One patient with paratyphoid B died in deep shock after an illness of twenty-four hours. The red cell volume was 60 per cent, the plasma volume only 40 per cent. The red cell count was 9,000,000 per cubic millimeter. Treatment was incapable of permanently filling the vascular system, the fluid administered actually left the vessels at the same rate, for the red cell count remained the same. A serious danger of shock which continues for a long time is anuria, which may become irreversible. I have observed this on a few occasions, once in a patient with diabetes, once in a patient with paratyphoid B. In both patients autopsy revealed nephrosis.

I saw a patient with paratyphoid B who had had severe diarrhea for two days. On admission there was severe shock. The skin was cyanotic, cold and moist. The patient had the hippocratic facies and did not respond to stimuli. His pulse rate was 160 to 170, his systolic blood pressure was 60 mm. On venipuncture I was struck by the treacly consistency of the blood. The hemoglobin level was 150 per cent, the red cell count 8,000,000 per cubic millimeter, the protein content of the plasma 6.72 per cent, the blood urea 2 Gm per liter and the alkali reserve 23 volumes per cent. On roentgen examination the heart was found very small. So I was dealing with shock from loss of plasma through the intestinal lesions. Intravenous drip treatment was instituted with the utmost speed. Two liters was introduced in two hours. The pulse became more easily palpable and the blood pressure rose to 90 mm systolic. The skin became warm and less cyanotic. Acidosis was combated with sodium bicarbonate. The man recovered his speech.

and gave the impression of having substantially improved. After the drip infusion was stopped the blood pressure fell again to 60 mm. The drip infusion was maintained for three days, the blood pressure rising to 120 systolic and 80 diastolic. The red cell count fell to 5,200,000 per cubic millimeter. The patient seemed well. It appeared, however, that only 40 to 60 cc of urine was excreted. Intense albuminuria developed, and the man died, the urea content of the blood being 5.5 Gm per liter. The pathologist observed nephrosis.

*Diabetes*¹⁰—The prognosis of diabetic coma depends on several factors. Prior to the introduction of insulin coma was an entirely hopeless condition, and even now it is serious, though fortunately there is today a possibility of saving the patient's life. On studying larger statistics one finds that the mortality from diabetic coma, in spite of expert insulin treatment, is still high. When one ascertains the kind of cases in which insulin has not the desired effect, various causes can be found to account for this circumstance. One of these causes is shock. I shall give an illustrative instance.

Five years ago, in the evening, a boy aged 15 was admitted to the department in deep coma. He had been unconscious for about four hours, the cause of the coma had been the omission of the necessary dose of insulin. There was no history of infection. With massive doses of insulin I succeeded toward midnight in getting the boy to "come around," the blood sugar had decreased considerably, and the alkali reserve had risen satisfactorily. The pulse was of good quality. Everything seemed favorable until, a few hours later, I was warned that the pulse was becoming poor. When I saw the boy the pulse could no longer be felt, and in a short time he died. At autopsy no explanation could be found for the sudden death.

Such a case, of course, did not fail to make a deep impression, especially as everything at first seemed to proceed well. This is, unfortunately, not the only instance I might cite. Now consider the way in which such an event can come about.

I then thought that the patient had collapsed suddenly. Later I became convinced of a more gradual development of such circulatory failure, which makes it possible to foresee the impending mischief by regularly observing the pulse and especially the systolic blood pressure. This value, which in diabetic coma is generally already low, gradually falls, attains a level of 80 to 70 to 60 mm and eventually becomes undeterminable.

If one regularly determines the red cell count in diabetic coma, one will nearly always find marked hyperglobulia. Moreover, by certain

¹⁰ Lawrence, R. D. *Brit. M. J.* **1** 690, 1930. Lande, H. *Uncontrollable Causes of Death in Diabetic Coma*, *J. A. M. A.* **101** 9 (July 1) 1933. Labbe, M., and Boulin, R. *Presse méd.* **41** 1705, 1933. Bethe, A., von Bergmann, G., Embden, G., and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1930, vol. 18, p. 634. Drabkin, D. L., and Edwards, D. J. *Am. J. Physiol.* **70** 273, 1924. Drabkin, D. L., and Shilkret, H. *ibid.* **83** 141, 1927.

methods based on the injection of dyes, one can demonstrate that the blood volume has actually decreased. The vascular system adapts itself as long as possible to the reduced blood volume, but if this diminishes too far the blood pressure will fall alarmingly. The cause of the concentration of the blood in diabetic coma is easily understood when one realizes that the patients always have considerable polyuria, and the loss of fluid is not compensated by drinking after the patient loses consciousness. Besides, if fluid can be taken, it is returned by vomiting. In spite of the serious dangers inherent in shock, one is not entirely powerless as to its treatment. As in so many chapters of clinical medicine, the rule holds that the most rapid intervention gives the best chance. What one is to do is obvious. Besides giving massive doses of insulin, one must apply measures to combat dehydration. I have adopted the rule of immediately administering 2 liters of physiologic solution of sodium chloride subcutaneously in every case of diabetic coma and, if necessary, repeating this procedure after a few hours. As soon as the patient can drink and does not vomit, I give fluids by mouth also. Meanwhile I carefully observe the blood pressure, which is read every half hour or even more frequently. When it falls, no profit will result from giving digitalis or other cardiac stimulants. One must try to raise the circulating blood volume in order to improve the diastolic filling of the heart and thus enable the heart to restore the blood pressure to normal levels. When in diabetic coma the blood pressure is very low, the blood sugar and the alkali reserve do not give a true picture of the condition. An immediate improvement, however, may result if one succeeds in raising the blood volume. I shall present an instance of shock associated with diabetic coma in which I succeeded in changing the condition for the better.

A girl aged 18 years was admitted unconscious to the department at 7 p. m. on June 20, 1934. She showed the typical picture of diabetic coma. The face was highly flushed, the respiration was of the "large" type. The maximal blood pressure was 120 mm and the minimal 75 mm. The blood sugar amounted to 514 mg per hundred cubic centimeters and the alkali reserve to 16 volumes per cent. The blood was distinctly concentrated, the red cell count being 6,000,000 per cubic millimeter. Immediately 100 units of insulin was injected. Two hours later the value for blood sugar had fallen to 375 mg per hundred cubic centimeters. Again 50 units were given. At 11 p. m. the blood pressure became lower, at midnight the pulse was hardly perceptible. The value for blood sugar at that time was 170 mg per hundred cubic centimeters. The picture of coma had now completely changed. The girl was still unconscious, her color was no longer red but pale and cyanotic. The respiration, instead of being deep and slow, had become rapid and shallow. The heart, on percussion, was not enlarged. The skin was cold, and the condition appeared alarming. Intravenous infusion was decided on. This was not easy, as the veins were so collapsed that I did not succeed in carrying out venipuncture. A vein had to be dissected free, after which a slow infusion of Bayliss' fluid was given. The pulse gradually became palpable. When 600 cc had been given, the blood pressure measured 150 systolic

and 80 diastolic. Epinephrine (1 mg) had been added to the fluid. The skin felt warm, and disappearance of the pallor and cyanosis was a further sign of an improved circulation. The condition at one stroke had changed for the better. Fortunately the improvement maintained itself, the blood pressure fell somewhat but remained within the limits of normal, and after a short time the patient spoke. She made a complete recovery. This girl's life was saved by refilling the vascular system and thereby restoring the circulation in good time.

I have not always succeeded in combating shock by restoring the blood volume with fluid and epinephrine. In the less favorable cases the infusion had a temporary effect, estimations showing the concentrated condition of the blood to have disappeared and the blood pressure to be reestablished, but after a few hours the values were seen to verge toward the alarming again. The quantity of urine produced during shock is generally small, which led me to assume that the fluid leaves the vessels and enters the tissues. At autopsy this is observed to be true, the organs being crammed with fluid. I recently observed such a case of shock, in which the fluid had drained from the vascular system. At autopsy the high fluid content of the abdominal viscera, lungs and subcutaneous fat was conspicuous. From the cut surface of the liver a pool of serous fluid collected in a short time.

The temporary nature of the effect of infusion of fluid might be ascribed to a too short duration of the effect of epinephrine. It is therefore certainly better to administer an intravenous drip infusion. At first until the pulse has improved, one may infuse rather rapidly, reducing the rate of the inflow to, say, 100 cc of fluid an hour, with 0.2 per cent of epinephrine solution. This is continued until the blood pressure shows no more tendency to fall. It may be necessary to maintain the drip infusion for a few days at a stretch, regulating the rate of inflow as required and taking the blood pressure as a guide.

Recently I saw a young man who had come under the treatment of his family physician only the day before. The physician asked for his admission to the hospital because of glycosuria. The same night the condition became worse, and on admission the next morning the patient was in deep shock (impalpable pulse, unmeasurable blood pressure, empty veins). Had he been treated only with insulin, he would surely not have lived much longer. An intravenous drip infusion pulled him through. Two hours later his blood pressure was normal, and the danger of shock was overcome. Meanwhile the acidosis was combated successfully with insulin.

Shock in diabetic coma does not always develop at the height of the comatose condition. It may develop after the patient has regained full consciousness, so that he falls back into coma. Several authors have even reported that shock may develop a few days after the patient has recovered from coma. I never saw this happen, but the possibility being recognized, careful observation of the pulse and blood pressure even when everything seems well is necessary for days. Apart from frank

coma, severe diabetic acidosis without impairment of consciousness may also lead to shock. In this connection I wish to mention the case of a little boy who, ambulatory, came to the clinic with entirely unimpaired sensorium but with a high blood sugar and a low alkali reserve. The blood was highly concentrated and the blood pressure low. I immediately admitted the boy to the inpatient ward and treated him with large doses of insulin. Five hours later typical shock developed, after the value for blood sugar had become normal and the alkali reserve had risen satisfactorily. The boy had been given 500 units of insulin.

The genesis of shock in diabetes is still unexplained. Probably the acidosis itself is not responsible, for shock is repeatedly seen to develop after ketosis has diminished or even after the ketone bodies have disappeared from the blood and urine. I have often been struck by the fact that in spite of clinical treatment the pulse may become steadily more rapid and weak and the blood pressure fall. It is remarkable that this should happen after admission of the patient to the ward, when one would expect the condition to improve as a result of the better management under which the patient is placed. The disturbance of metabolism is dealt with by massive doses of insulin. Why, then, does shock develop?

There is some reason to suspect that the insulin is responsible for this. It is well known that injections of insulin, both in healthy and in diabetic persons, at first may lead to a marked increase in weight. This increase is caused by retention of water in the tissues. Edema may develop not from renal insufficiency but from purely extrarenal causes. In many diabetic persons one sees slight to moderate inspissation of the blood after the first injections of insulin. Under the action of insulin, water and salts leave the blood stream and are absorbed in the tissues. This, at least, is found during the first few hours or, at most, days of the insulin cure. Later, after the tissues have become saturated with fluid, the concentrated state of the blood disappears and even gives way to dilution. Thus some kind of balance is established. The concentration of the blood is more marked as the diabetes is more severe, the doses of insulin higher and the fall of the value for blood sugar more steep.

The concentration of the blood is most marked in hypoglycemic shock. Drabkin has proved this in experiments on dogs. I had an opportunity of examining schizophrenic patients during insulin shock induced therapeutically. I observed an increase of concentration of the blood, which could be shown by a rise of the protein content of the plasma and the red cell count. On one occasion I even saw the latter rise in a few hours from 4,900,000 to 6,300,000 per cubic millimeter. Drabkin was able to prove with dogs that the concentration of the blood was much more marked when the animals had previously

been brought into a state of dehydration by withdrawal of fluid from their diet. This evidence perhaps explains to some degree the development of shock in my diabetic patients. By the action of insulin the capillaries become permeable to water, the circulating blood volume decreases, the blood pressure falls and the previously described condition of shock is produced.

Schittenhelm in 1927 drew attention to the remarkable difference between patients who died in diabetic coma in the period before insulin came into use and those who now die from this cause after having been treated with insulin. Formerly, intense polyuria persisted to the last, whereas now anuria is conspicuous. This observation must be true. I have repeatedly observed patients admitted to the ward with full bladders, in whom, afterward, severe oliguria or even anuria developed. Probably both anuria and shock are the result of loss of fluid from the capillaries.

If it is true that insulin produces or perhaps aggravates shock, this is distressing, but for the present there is no means of preventing it with certainty. One can only urge physicians to be careful in giving large doses of insulin at once, if not strictly necessary. In treating a patient for fully developed coma the administration of large doses of insulin cannot be dispensed with, in treating for precoma, which is not such an emergency, it is better to give small hourly doses instead of larger doses at longer intervals. Under these conditions protamine zinc insulin may be valuable. It has been shown experimentally that this careful administration of insulin gives less rise to increased permeability of the vessel walls. It seems important, therefore, not to let the blood sugar level fall too rapidly. It can safely be left high, and the administration of sugar in case of a marked fall (perhaps even at the onset of treatment) will help in preventing shock. In clearcut diabetic coma, in which there is no time to lose, careful dosage may not be ventured. One must try as soon as possible to mend the state of dehydration by compensating for the loss of fluid from the vascular system in every accessible way. Regularly repeated counts of the erythrocytes indicate the progress of the dehydration, but the most important measure, in my opinion, is regular observation of the blood pressure. If it is very low or falls during treatment, one must not delay but must attempt to refill the vascular system.

Fatal shock in diabetic coma is more frequent in elderly persons than in the young. An analogous behavior is seen in severe gastric hemorrhage, which in elderly persons with arteriosclerosis is more dangerous than in subjects with healthy vessels. It is possible that this is due to the fact that a heart with narrow coronary vessels is more susceptible to a too low blood pressure than a normally vascularized heart.

Addison's Disease—In Addison's disease, together with a low arterial pressure, a normal venous pressure is found. During the crises, however, the arterial pressure is reduced still further, and the venous pressure also falls. In adrenalectomized animals the circulating blood volume is considerably reduced. An extract of adrenal cortex may abolish this shock. During the crises in clinical cases I have also repeatedly observed a raised red cell count (up to 7,000,000) and a raised level of plasma protein. This condition can generally be adequately dealt with by the use of an extract of adrenal cortex alone. Fluid is of no use, as it leaves the vascular system. It is probable, therefore, that in adrenal failure the mechanism that keeps the quantity of circulating blood on a constant level is disturbed. This disturbance probably should be ascribed to loss of sodium, which in adrenal insufficiency is eliminated through the kidneys, carrying water with it. The sodium also escapes into the tissues, together with water. An extract of adrenal cortex can repair this disturbed regulation of the distribution of fluid between blood and tissues. The shock associated with adrenal failure is so well understood that the deduction has been drawn that in other forms of shock adrenal failure should be assumed. It is questionable, however, whether the similarity of the syndromes should induce one to assume a similarity of causes. If extract of adrenal cortex can bring about improvement in cases of shock of other types, this is no proof that adrenal failure is in play in all kinds of shock. Heuer and Andres studied shock occurring in animals after injection of extracts of putrefying intestinal contents. They found the typical picture of shock, with concentration of blood and extravasation of plasma. On injecting fluid they obtained no improvement, the fluid leaving the vessels. When they gave extract of adrenal cortex simultaneously with the fluid, good results were obtained, the blood pressure and plasma volume becoming normal. This does not necessarily mean that the shock brought about by these investigators was due to adrenal failure. I have repeatedly met with patients for whom the infusion of fluids was of no avail, the blood pressure remaining low and the concentration of the blood being little influenced. This shows only that the vessels are damaged to such a degree that the fluid drains away through their walls. I have therefore tried to give substances reducing the permeability of the vessel walls. Calcium, parathyroid extract and dihydrotachysterol (A. T. 10) were tried, without the least benefit. Success was often obtained by adding epinephrine, paramethylaminoethanolphenol tartrate (sympatol) or ephedrine to the fluid. It is possible that constriction of the vessels reduces their permeability. On a few occasions, however, I have seen good results from the use of an extract of adrenal cortex. This was true in the case of a patient in anaphylactic shock, who was given an intravenous drip infusion and

did not respond in spite of large quantities of fluid and epinephrine. Whether post hoc or propter hoc, administration of an extract of adrenal cortex was followed by improvement. The similarity of shock and adrenal crisis may be such that mistakes can be made.

Five years ago my advice was asked for a woman who had been admitted to the surgical department because of a condition diagnosed as ileus. She had a rapid pulse and a blood pressure of 70 to 80. Her skin was distinctly pigmented. I did not hesitate to make a diagnosis of Addison's disease. Uremia (blood urea 7 Gm per liter) was present, but I did not consider this an uncommon feature, as the patient had vomited a great deal. After an initial improvement under the influence of extract of adrenal cortex, the woman died. No changes were found in the adrenal glands, but to my amazement and that of my associates there were typical contracted kidneys. For a long time I was unable to explain this. It was only after improving my knowledge of shock that I found the solution. This woman had contracted kidneys and became uremic, and as a result of this she began to vomit severely. This caused shock, as was shown by the pulse and blood pressure. Although the skin of chronically nephritic persons is occasionally pigmented, the remarkable pigmentation in this case, added to the other symptoms, had led me astray.

A woman aged 45 had been ill for five weeks. She had high fever and disturbed micturition. The urine contained much pus. I was called because her heart action was bad. I found her in typical shock, lying flat in bed, with a rapid pulse (almost impalpable) and a blood pressure of 80 mm systolic. The nose was cold. There was marked cyanosis. There was no enlargement of the heart. A roentgenogram taken from a distance of 1 meter with the patient supine showed a small heart, the maximal diameter being 9.5 cm. There were no pigmentations. I made a diagnosis of shock, the cause of which I did not know. I thought of infectious shock because of the severe pyelitis. It was peculiar and characteristic of the ever similar picture of shock that a head nurse remarked "If I didn't know better, I should say she is in diabetic coma." The erythrocyte count was 8,060,000 per cubic millimeter. The alkali reserve was 30 volumes per cent, the blood urea 3 Gm per liter. By infusion of Bayliss' fluid and Ringer's solution and epinephrine I succeeded in overcoming the shock, the blood pressure rose to 120 systolic and 80 diastolic, the pulse became more easily palpable and slower, and the erythrocyte count fell to 4,700,000 per cubic millimeter. Meanwhile, tubercle bacilli were found in the urine. It was only then that the possibility of Addison's disease was considered. The sodium content of the blood was 285 mg per hundred cubic centimeters. An extract of adrenal cortex was administered. The patient died, and besides unilateral renal tuberculosis there was observed bilateral caseating tuberculosis of the adrenal glands.

A patient was admitted in a dehydrated condition, with a very low blood pressure and a rapid pulse. At home she had vomited a great deal. She was slightly uremic, the blood was concentrated. In view of the marked emaciation I first thought of cancer of the stomach. With the former cases in mind, however, I thought also of Addison's disease. A very low level of blood sodium sustained this presumption, and treatment with an extract of adrenal cortex brought immediate relief. After this extract was withdrawn the condition became worse. On a diet with much salt and little potassium the woman did well. A close examination did not reveal carcinoma.

These cases show that shock for which no certain cause can be demonstrated should always suggest Addison's disease even in the absence of pigmentation, which absence, in my experience, is anything but rare

Acute Pancreatitis—Shock is a common symptom of acute pancreatitis. I saw a woman who had high fever shortly after obstetric delivery, with abdominal pain, which, however, was not prominent. She was in severe shock. No cause was known. During the preparation for an infusion she died. At autopsy extensive pancreatitis with fat necrosis was observed. In cases of pancreatitis high red cell values, up to 9,000,000, are often found. The cause of shock in this case is not known, that histamine-like substances were liberated from the necrotic tissues is suggested as a possibility.

Acute Peritonitis—The facies hippocratica so often described in cases of acute peritonitis is an expression of shock. In these cases a reduced circulating blood volume is always found. This shock is clearly understood when one keeps in mind the stagnation of blood in the capillaries over so great a surface as the peritoneum. Besides, there is exudate, which means an escape of plasma through the walls of the blood vessels.

Combustion and Congelation—In these conditions the reduction of the blood volume is the result of extravasation of plasma. Excessive rise of hemoglobin is found, with a normal level of plasma protein. Underhill once found 230 per cent of hemoglobin. In congelation the findings are materially the same. In the treatment of these conditions the management of shock deserves more consideration than has generally been given it.

Anaphylaxis—I observed a considerable rise of the red cell count during extensive serum disease in 2 cases.

A patient with ulcerative colitis was treated with large quantities of dysentery serum. After receiving the last injection of 80 cc she had an extensive serum rash, occupying practically the whole cutaneous surface. The pulse was impalpable, and the blood pressure could not be measured. The clinical impression was that of shock. The red cell count, determined a few days before at 4,500,000, rose in a few hours to 6,000,000. It was remarkable how I failed to determine the circulating blood volume. When congo red was injected, it immediately disappeared from the blood and was stored in the urticarial wheals, which became fiery red. One can hardly imagine a better demonstration of the permeability of the vessels. For this patient an intravenous drip infusion was established. The blood pressure kept falling over and over again until the third day, when it was maintained on a constant level, perhaps by the simultaneous administration of 50 cc of an extract of adrenal cortex. Until then the fluid had run away through the vessel walls in spite of the addition of epinephrine, as was seen from the grave edema that had developed.

A patient with ulcerative colitis was given a blood transfusion from a donor of the same blood group, the samples mixing without agglutination. Fifteen

minutes after the transfusion generalized urticaria developed. The blood pressure was 50 mm systolic, and the pulse was rapid. There was a clinical picture of shock, though not severe. The erythrocyte count previously had been 3,900,000 per cubic millimeter. During the shock it was 7,000,000. The protein content of the plasma was 6.34 per cent. A few hours later, after the shock had passed, these values were respectively 4,900,000 and 6.12 per cent, hence there had occurred exudation of plasma. The patient, a woman, was treated only with 50 cc of extract of adrenal cortex, the shock was over in two hours, whether or not as a result of this treatment, I do not know.

TREATMENT

In briefly summarizing the treatment, I may state that cardiotonics do not accomplish anything, which means that they should be left alone. Certain attempts may, however, be made to combat shock. One may try to stimulate the vasomotor system, for instance, with carbon dioxide. The administration of carbon dioxide should always be combined with that of oxygen, as acapnia by itself might cause shock. Loss of heat must be avoided, the blood volume is augmented by warmth. As medicines, one may give strychnine, metrazol, caffeine or camphor. I have never had an impression that they helped. As peripheral vascular stimulants, one may try epinephrine, paramethylaminoethanolphenol tartrate (sympatol), ephedrine and solution of posterior pituitary. These drugs, in my experience, are helpful principally if introduced directly into the blood together with much fluid. As shock is based on reduced blood volume, there can be only one causal treatment: replenishment of the deficient blood volume. In treating for shock from hemorrhage I have used blood, in treating for shock from other causes, Ringer's solution, or saline solution if the chloride value is low. Bayliss' fluid may be tried if the viscosity of the blood is not increased. Acidosis is combated with alkalis. Attempts may be made to improve the relation of fluid in the vascular system, e. g., with substances that act on the peripheral blood vessels or with substances that lessen the permeability of the vessels (perhaps an extract of adrenal cortex).

INCIDENCE OF FATAL CARDIOVASCULAR DISEASE IN CHARLESTON, S C

WITH PARTICULAR REFERENCE TO HYPERTENSION

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A series of 2,066 consecutive autopsies performed by the staff of the department of pathology of the Medical College of the State of South Carolina from Jan 1, 1928 through May 1938 has been reviewed by us as a statistical study of cardiovascular disease in the South, particularly among American Negroes. Instances of trauma to the heart or vessels have been excluded, but all other cases are included.

During this period all the autopsies done in the County of Charleston were performed by a member of this staff, including investigations authorized by the coroner in cases of sudden death. Furthermore, since most of the cases prior to about 1935 were from the charity services of the Roper Hospital—a general county hospital for white persons and Negroes—there has been little or no migration of patients, and the results as given here can be taken as representative of fatal cardiovascular disease in this area, at least in the Negro. During this period of ten years the autopsy rate in this hospital has risen from about 25 to about 50 per cent. Since about 1935 the autopsy rate for the white and that for the Negro group have been about equal, while prior to that time the autopsy rate for the white patients, especially those not dependent on charity for hospitalization, was low. Hence the figures for the white race prior to 1935 may not be truly representative.

In 518 of the 2,066 cases (25.07 per cent of the total number of autopsies) death was thought to be a direct or indirect result of cardiovascular disease, while in 106 other cases the changes relative to the cardiovascular system were thought to be more or less incidental, and not themselves the cause of death. The corresponding clinical records

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were also studied, and pertinent data were recorded. The cases were then classified on an etiologic basis.

CRITERIA FOR CLASSIFICATION

The term congenital heart disease, as used here, does not include patent ductus arteriosus or patent foramen ovale in infants. Four cases of perforate interventricular septum (in 2 of which there were other congenital cardiac anomalies) and 1 case of transposition of the aorta and the pulmonary artery were encountered. Numerous other relatively minor congenital defects were observed, none of which was thought to be the cause of death.

The accurate definition of criteria for the diagnosis of hypertensive cardiovascular disease was difficult. It is known that the blood pressure may be temporarily raised to hypertensive levels without actual cardiovascular disease being present. Furthermore, some patients admitted with congestive heart failure or in some other terminal state may not show clinical hypertension, although the patient is known to have had high blood pressure previously and shows evidence of hypertensive cardiovascular disease at autopsy. Hence the level of blood pressure as the sole determining factor is not always a satisfactory criterion. Some patients show no appreciable hypertrophy of the heart at autopsy, although clinical hypertension has been present for several years. Finally, some persons show hypertension clinically and hypertrophy of the heart, but the kidneys reveal little gross or microscopic change. No single factor seems adequate for the classification of cases in this group. We have adopted three criteria for the postmortem classification of cases of hypertensive cardiovascular disease, viz:

1. Clinical evidence of hypertension during life (diastolic pressure of 100 mm or above, or systolic pressure of 160 mm or above provided the diastolic pressure is not below 70 mm.)

2. Cardiac hypertrophy without valvular faults (weight of heart above 500 Gm.)

3. Contracted kidneys (weight 125 Gm. or less), with microscopic evidence of arteriosclerosis.

With few exceptions, in the cases classified here as those of hypertension at least two of these features have been shown. About 5 cases have been included in which the conditions met only one of these rigid requirements, but came close to the other two. These fitted into no other classification and appeared to belong in this group. Cases in which the criteria just listed were met but the patients died of some condition other than cardiovascular disease are not included in the tables under this heading. Unless there was evidence of congestive heart

failure, of uremia or of vascular accident the hypertension was regarded as incidental

In the third group, that of cases of atherosclerotic disease, are included instances in which there was no evidence of hypertensive disease as already listed and death was the result of advanced arterial lesions. Cases in which there were pronounced arterial changes, without evidence of hypertension at the time of death, and the patient died of coronary occlusion, cerebral hemorrhage, mesenteric thrombosis or the like are included in this group.

In the group of cases of syphilitic cardiovascular disease there were patients dying of syphilitic aortic valvulitis with congestive heart failure, from occlusion of the ostia of the coronary arteries by syphilitic scars and plaques in the aorta, from syphilitic aneurysm (causing death by rupture and hemorrhage or by compression of vital structures) and from syphilitic myocarditis. The last diagnosis is open to criticism, since in only 1 instance, a case of congenital syphilis, were spirochetes demonstrated in the myocardium. The patients whose condition was so diagnosed had strongly positive Kolmer and Kahn reactions antemortem and showed inflammatory lesions in the myocardium of a chronic nature.

The group of patients with rheumatic heart disease includes those dying of active rheumatic carditis and those dying as a result of residual scars in the valves and myocardium of rheumatic origin which resulted in congestive heart failure.

In the group of cases of "inflammatory" heart disease are included those of acute and subacute bacterial endocarditis, a few cases of severe acute myocarditis, cases of tuberculous pericarditis, in which death apparently resulted from cardiac embarrassment rather than from tuberculous infection and cases of fatal acute pericarditis without other evidence of vascular disease. Cases of syphilitic cardiovascular disease and of rheumatic carditis are not included here. Cases of adherent pericardium of unknown cause are listed under this heading, but when the pericarditis could be shown to be tuberculous in origin it was so classified.

The group of cases of chronic pulmonary disease with heart failure includes cases of pulmonary fibrosis from the inhalation of irritant dusts (particularly asbestos in this locality) and cases of emphysema following asthma and other conditions in persons dying of congestive heart failure for which no other cause could be found.

The grouping of cases of vitamin B₁ deficiency under cardiovascular disease is open to question, but each of the children whose condition was so diagnosed apparently died of vascular failure, showed a large heart and had a more or less definite history of vitamin deficiency.

TABLE 1—*Relative Incidences of the Various Etiologic Types of Cardiovascular Disease According to Race and Sex Observed at 518 Consecutive Autopsies in Cases of Fatal Cardiovascular Disease*

Type	Males				Females				All White Patients		All Negro Patients		All Males		All Females		All Patients	
	White		Negro		White		Negro		No	%	No	%	No	%	No	%	No	%
	No	%	No	%	No	%	No	%										
	No	%	No	%	No	%	No	%										
Congenital heart disease	1	2.1	2	0.7	0	0	2	1.3	1	1.5	4	0.9	3	0.9	2	1.2	5	1.0
Hypertensive vascular disease	16	34.0	186	62.6	7	33.3	80	52.3	23	33.8	266	59.1	202	53.7	87	50.0	289	55.8
Arteriosclerotic disease	16	34.0	14	4.7	6	28.5	18	11.8	22	32.1	32	7.1	30	8.7	24	13.8	54	10.4
Syphilitic vascular disease	3	6.4	51	17.2	0	0	13	8.5	3	4.1	64	14.2	54	15.7	13	7.5	67	12.9
Rheumatic heart disease	3	6.4	7	2.4	2	9.5	10	6.5	5	7.1	17	3.8	10	2.9	12	6.9	22	4.3
"Inflammatory" heart disease	8	17.0	29	9.8	5	23.8	28	18.3	13	19.1	57	12.7	37	10.8	33	19.0	70	13.5
Heart failure due to pulmonary disease	0	0	6	2.0	1	4.8	1	0.7	1	1.5	7	1.6	6	1.7	2	1.2	8	1.5
Beriberi heart	0	0	2	0.7	0	0	1	0.7	0	0	3	0.7	2	0.6	1	0.6	3	0.6
Total number	47	99.9	297	100.1	21	99.9	153	100.1	63	100.1	450	100.1	344	100.0	174	100.2	518	100.0

ETIOLOGIC CLASSIFICATION OF CASES

The cases of fatal cardiovascular disease are classified in table 1 as to etiologic type, race and sex

Perusal of this table reveals several noteworthy facts. The incidence of hypertensive cardiovascular disease is exceedingly high, especially in the Negro, being almost twice as common, sex for sex, as in the white race. Among Negro males it comprises 62.6 per cent of all cases of cardiovascular disease, and the incidence is only slightly lower (52.3 per cent) for Negro females. Among white males hypertensive cardiovascular disease accounts for 34 per cent of the cardiovascular deaths, and among white females, for 33.3 per cent. In white males arteriosclerosis (without hypertension) is as commonly a cause of death as is hypertension, but in Negro males arteriosclerosis accounts for a relatively small proportion of deaths. As would be expected from the relatively

TABLE 2—*Sexual Differences in Incidence of Etiologic Types of Cardiovascular Disease*

Etiologic Type	Males, Percentage	Females, Percentage
1 Congenital heart disease	60.0	40.0
2 Hypertensive cardiovascular disease	69.9	30.1
3 Arteriosclerotic disease	40.7	59.3
4 Syphilitic cardiovascular disease	80.6	19.4
5 Rheumatic heart disease	45.5	54.5
6 "Inflammatory" heart disease	52.9	47.1
7 Heart failure due to pulmonary disease	75.0	25.0
8 Beriberi heart	66.7	33.3
All types	66.4	33.6

high rate of syphilis among Negroes, syphilitic cardiovascular disease is an important cause of death in that race, while in the white race it is much less common.

In table 2 the total number of cases in each etiologic group is distributed between the sexes. The number of cases in groups, 1, 5, 7 and 8 is too small for the figures to be significant. In the other classifications the figures are probably reasonably representative. Hypertensive cardiovascular disease is more than twice as common in the male as in the female, and syphilitic cardiovascular disease is four times as common in the male. Arteriosclerotic disease is slightly more frequent in the female than in the male. All types of cardiovascular disease combined are twice as common in the male as in the female.

The large group of patients with hypertension (white, 23, Negro, 266) is divided further in table 3 as to the actual manner of death. The average age at death for each group is also included. (In the Negro race the age given by the patient is frequently unreliable. It is not uncommon for a gray-haired, edentulous Negro man to give his age as 22. This was corrected in so far as possible by comparing the

stated age with the estimated age at death. If the two agreed within a decade, the stated age was taken to be correct, since the limits of error of the estimation are rather wide. If the estimated age exceeded the stated age by more than a decade, the former was taken to be correct.)

In many cases of hypertensive cardiovascular disease autopsy revealed more than one of the factors previously listed. Cases of combined factors are listed under the heading of the condition which seemed to have caused the death (i. e., rupture or dissection of the aorta took precedence over all other classifications, cerebral hemorrhage came next, then coronary thrombosis).

TABLE 3—*Manner of Death in 289 Cases of Fatal Hypertensive Cardiovascular Disease, with Age at Death*

Cause of Death	White Patients			Negro Patients			All Patients		
	No	Per centage	Aver age	No	Per centage	Aver age	No	Per centage	Aver age
Uncomplicated, with heart failure	8	34.8	61	97	36.5	51	105	36.3	52
Azotemia *	7	30.4	46	64	24.1	44	71	24.6	44
Uremia * and edema	2	8.7	43	22	8.3	41	24	8.3	41
Coronary thrombosis	1	4.4	48	9	3.4	45	10	3.5	45
Cerebral hemorrhage or thrombosis	4	17.4	65	57	21.4	49	61	21.1	50
Thrombotic gangrene (of extremity, etc.)	1	4.4	55	5	1.9	51	6	2.1	51
Hypertension plus aortic insufficiency (usually syphilitic) with heart failure	0	0		9	3.4	41	9	3.1	41
Rupture or dissection of aorta	0	0		3	1.1	43	3	1.0	43
	23	100.1	55	266	100.1	47	289	100.0	48

* Azotemia or uremia, as employed here, signifies an elevation of the urea nitrogen in the blood to 50 mg. per hundred cubic centimeters or above, or of the creatinine to 5 mg. per hundred cubic centimeters or above, together with other evidences of uremia (clinical and at autopsy).

It is worthy of note in this table that while the incidence of hypertensive cardiovascular disease is much greater in the Negro than in the white group, the manner of death for the two groups is about the same. The high incidence of uremia as a manner of death is shown. In each group it can be noted that the Negro died at an earlier age than did the white man. It is especially noteworthy that the Negro died of apoplexy, associated with hypertension, sixteen years earlier than the white man.

That aortic insufficiency and hypertension may occur together in the same case has received scant notice in the literature. In such cases the diastolic pressure may fall below the level generally taken to indicate hypertension, but the systolic pressure tends to remain high. The average of the highest systolic blood pressures recorded in these cases was 205 mm., that of the highest diastolic blood pressures, 100 mm. In almost all these cases the condition was diagnosed clinically as aortic

insufficiency due to syphilis, although in some it was diagnosed as hypertensive cardiovascular disease when the murmurs in the aortic area were not characteristic. In 7 of the 9 cases in which aortic insufficiency was associated with hypertension, the insufficiency was due to syphilitic scarring of the aortic valves and commissures. In the other 2 cases it appeared that there had been an incomplete transverse rupture of the aorta just above the commissures of the aortic valve, similar to the intimal rupture that occurs in dissecting aneurysm, the active process of rupture had healed, leaving a slitlike gap in the aortic wall, covered by endothelium, which permitted the aortic cusps to fall back into the ventricle during diastole. In both these cases there were the typical aortic diastolic murmur of aortic insufficiency and the wide pulse pressure that goes with that condition. One of these patients, several months before his admission to the hospital, had suffered severe sub-

TABLE 4—*Manner of Death in 54 Cases of Fatal Arteriosclerotic Disease (Without Evidence of Hypertension), with Age at Death*

Cause of Death	White Patients			Negro Patients			All Patients		
	No	Per centage	Average Age	No	Per centage	Average Age	No	Per centage	Average Age
Generalized arteriosclerosis (without hypertension) as a cause of death	9	40.9	73	12	37.5	67	21	38.9	70
Coronary thrombosis without hypertension	8	36.4	59	4	12.5	65	12	22.2	61
Other vascular accident without hypertension	5	22.7	59	16	50.0	56	21	38.9	57
	22	100.0	65	32	100.0	61	54	100.0	63

sternal pain. This had subsequently disappeared, although the cardiac failure, as manifested by edema, did not occur until a day or so after the pain. This pain may well have been the time at which the short dissection (if we may call it that) occurred.

It is interesting to note that the incidence of syphilitic aortic insufficiency for the total group of hypertensive patients was 2.06 per cent, for the whole autopsy group it was 2.23 per cent.

The group of 54 cases of fatal arteriosclerotic disease (22 white persons, 32 Negroes) is subdivided in table 4 according to the manner of death. It can be seen that coronary thrombosis without hypertension is relatively rare in the Negro, but that other vascular accidents are extremely common. In the whole series of cases of fatal cardiovascular diseases, hypertensive and nonhypertensive, there were 13 cases (2.9 per cent) of coronary thrombosis in the Negro and 9 cases (13.2 per cent) in the white. In two thirds of the cases of coronary thrombosis among Negroes the condition was associated with evidence of hypertension, but in only one ninth of those in the white group was the dis-

ease thought to be associated with hypertension. Likewise, in the whole group of cases of fatal cardiovascular disease death was from vascular accident other than coronary in 10 cases (14.7 per cent) of the white group and in 81 cases (18 per cent) of the Negro group (Cerebral hemorrhages due to tumor of the brain, congenital aneurysms and the like are not included). In the white group half of the vascular accidents other than coronary occurred without evidence of hypertension at the time of death, but in the Negroes more than 80 per cent of the vascular accidents other than coronary occurred with evidence of hypertension. Most of the cases of "vascular accident" listed here were instances of cerebral hemorrhage or thrombosis. This accident seems to occur in the Negro more than ten years earlier than in the white person.

Syphilitic cardiovascular disease was the cause of death in 67 patients, 64 of these were Negroes and 3 white persons. The cases are

TABLE 5—*Manner of Death in 67 Cases of Fatal Syphilitic Cardiovascular Disease, with Age at Death*

Cause of Death	White Patients			Negro Patients			All Patients		
	No	Per centage	Average Age	No	Per centage	Average Age	No	Per centage	Average Age
Syphilitic aortic insufficiency with heart failure	0	0		29	45.3	39	29	43.3	39
Narrowing of coronary ostiums by syphilitic plaques in the aorta	2	66.7	42	9	14.1	45	11	16.4	44
Fatal syphilitic aneurysm of any vessel	1	33.3	45	21	32.8	43	22	32.8	43
Syphilitic myocarditis	0	0		5	7.8	28	5	7.5	28
	3	100.0	43	64	100.0	40	67	100.0	40

subdivided in table 5 according to the manner of death. (Frequently two or more of these conditions were combined in a single case. If so, the case has been listed under the condition thought most likely to be the cause of death, thus, a ruptured aneurysm took first preference, syphilitic narrowing of the coronary ostiums second and syphilitic aortic insufficiency third.)

It is obvious that the number of cases of syphilitic cardiovascular disease in the white race is too small for any interpretation to be placed on their distribution among groups. In the Negroes syphilitic aortic valvulitis, with insufficiency and congestive heart failure, was the commonest cause of death, although aneurysm was frequently an important factor. In the few cases of syphilitic narrowing of the coronary ostiums which were encountered, death was usually sudden, occurring particularly during exertion or emotional strain, and unless the lesion was associated with insufficiency of the aortic valve, there was usually no evidence of edema. A great many cases of uncomplicated syphilitic aortitis were encountered in this series, but in none was it the cause

of death Wilson¹ studied the cases of syphilitic aortitis in this service during the period covered by this study and has reported on them

Rheumatic heart disease was the cause of death in 22 cases, 5 of the patients were white and 17 Negroes, with the distribution shown in table 6. Rheumatic heart disease is relatively rare in Charleston, although the incidence varies somewhat from year to year. The number of cases is about evenly divided between patients dying during

TABLE 6—*Manner of Death in 22 Cases of Fatal Rheumatic Cardiovascular Disease, with Age at Death*

Cause of Death	White Patients			Negro Patients			All Patients		
	No	Per centage	Average Age	No	Per centage	Average Age	No	Per centage	Average Age
Active rheumatic carditis	2	40	11	9	52.9	20	11	50	18
Rheumatic sequelae with heart failure	3	60	54	8	47.0	26	11	50	34
	5	100	37	17	99.9	23	22	100	26

TABLE 7—*Manner of Death in 70 Cases of Fatal "Inflammatory" Cardiovascular Disease (Nonrheumatic, Nontuberculous), with Age at Death*

Cause of Death	White Patients			Negro Patients			All Patients		
	No	Per centage	Average Age	No	Per centage	Average Age	No	Per centage	Average Age
Acute bacterial endocarditis	6	46.2	48	11	19.3	43	17	24.3	45
Subacute bacterial endocarditis	2	15.4	20	2	3.5	35	4	5.7	27
Acute myocarditis	1	7.7	75	9	15.8	33	10	14.3	37
Tuberculous pericarditis	0	0		18	31.6	37	18	25.7	37
Acute pericarditis (nonrheumatic, nontuberculous)	3	23.1	36	13	22.8	26	16	22.9	28
Adhesive pericarditis	1	7.7	65	3	5.3	45	4	5.7	50
Chronic myocarditis*	0	0		1	1.8	35	1	1.4	35
	13	100.1	44	57	100.1	35	70	100.0	37

* A case of chronic inflammatory disease of the myocardium of unknown origin, apparently not syphilitic

the active stage of inflammation of the heart and those dying as a result of residual effects (usually mitral stenosis). Although our total number of cases is small, and therefore may not be representative, the process seems to affect the white race relatively more than the Negro.

The group of "inflammatory" heart disease (nonrheumatic and non-syphilitic) comprised 70 cases, 13 of white persons and 57 of Negroes. They are classified in table 7.

1 Wilson, R., Jr. Studies in Syphilitic Cardiovascular Disease. I. Uncomplicated Syphilitic Aortitis, an Asymptomatic Condition, *Am J M Sc* **194** 178, 1937.

It can be seen that tuberculosis of the pericardium was not the cause of a single death from heart failure in the white group, but was a relatively common cause of death in the Negro group. This corresponds with the much higher incidence of tuberculous infection in the Negro than in the white population in this region. Even when allowance is made for the difference in the total number of cases in the two races due to the high incidence of tuberculous pericarditis, it seems that acute and subacute bacterial endocarditis are more common in the white than in the Negro race. No obvious explanation for this is apparent, it may reflect merely the greater interest of the resident staff in securing autopsies on that group of the white patients, while in the cases of cardiovascular disease that seemed to be of less interest clinically per-

TABLE 8—*Relative Incidence of the Various Types of Cardiovascular Disease Causing Death by Heart Failure*

Cause of Death	White Patients		Negro Patients		All Patients	
	No	Percentage	No	Percentage	No	Percentage
Congenital heart disease	1	3.7	4	1.8	5	2.0
Hypertensive cardiovascular disease	9	33.3	119	53.1	128	51.0
Hypertensive disease plus valvular disease	1	3.7	10	4.5	11	4.4
Hypertensive disease plus coronary thrombosis	1	3.7	9	4.0	10	4.0
Coronary thrombosis, without hypertension	8	29.6	4	1.8	12	4.8
Syphilitic aortic insufficiency	0	0	29	12.9	29	11.6
Syphilitic narrowing of coronary ostia	2	7.4	9	4.0	11	4.4
Syphilitic myocarditis	0	0	5	2.2	5	2.0
Rheumatic heart disease (residual effects)	3	11.1	7	3.1	10	4.0
Tuberculous pericarditis	0	0	18	8.0	18	7.2
Adhesive pericarditis	1	3.7	3	1.3	4	1.6
Chronic pulmonary disease with heart failure	1	3.7	7	3.1	8	3.2
Total no	27	99.9	224	99.8	251	100.2

mission for autopsy was not urged. The higher percentage of autopsies among the Negroes than among the white patients in the earlier part of the period covered by this study has already been alluded to.

In table 8 we have listed all cases of death from heart failure, without acute infectious disease, under the headings of the various etiologic factors. The great importance of hypertension as a cause of congestive failure in this locality is shown, especially in the Negro. In the white race coronary thrombosis (when the cases of hypertensive and those of nonhypertensive coronary thrombosis are combined) equals hypertensive cardiovascular disease in importance, in the Negro coronary thrombosis is relatively uncommon. Syphilitic cardiovascular disease causes heart failure more than twice as often in the Negro as in the white race. No case of syphilitic aortic valvulitis with insufficiency was encountered in the series of autopsies on white patients. Rheumatic heart disease seems to be more frequently a cause of congestive failure

in the white than in the Negro group, but the number of cases is too small for the conclusion to be definite

Table 8 can be compared with tables prepared by authors in other localities, in which the relative incidence of the various types of heart disease is given. Such comparison must be made with great caution, however, since many factors are involved. Most of the studies available for comparison are clinical, and relatively few autopsy data can be found in the literature. The economic status of the patient, the nature of the cardiac service from which the results were reported and racial factors are only some of the many factors that must be considered in making comparisons. In comparing autopsy statistics on the subject, the autopsy rate in the hospitals concerned and the criteria for diagnosis are important. It is especially important to know whether cases of sudden death are included, as in the cases commonly examined by a medical examiner or coroner.

Suffice it to say at this point that the incidence of hypertensive cardiovascular disease has been shown to be high, especially in the Negro, in studies from Texas,² Georgia,³ Tennessee,⁴ the District of Columbia⁵ and San Francisco.⁶ In New England,⁷ New York city⁸ and the Rocky Mountain region⁹ rheumatic heart disease is of relatively more importance than is hypertensive disease. Whether this means that hypertensive cardiovascular disease in these areas is actually less frequent in the population than it is in the Southern areas, or whether the high incidence of rheumatic heart disease (which is known to be regional in

2 Stone, C. T., and Vanzant, F. R. Heart Disease as Seen in a Southern Clinic. A Clinical and Pathological Survey, *J. A. M. A.* **89** 1473 (Oct. 29) 1927.
Schwab, E. H., and Schulze, V. E. The Incidence of Heart Disease and of the Etiological Types in a Southern Dispensary, *Am. Heart J.* **7** 223, 1931.

3 Davison, H. M., and Thoroughman, J. C. A Study of Heart Disease in the Negro Race, *South. M. J.* **21** 464, 1928.

4 Laws, C. L. The Etiology of Heart Disease in Whites and Negroes in Tennessee, *Am. Heart J.* **8** 608, 1933.

5 Gager, L. T., and Dunn, W. L. Heart Disease in Washington, D. C. A Study of Etiologic Types and the Factors of Race, Age and Sex in One Thousand and Two Hundred Cases, *M. Ann. District of Columbia* **2** 112, 1933.
Hedley, O. F. A Study of Four Hundred and Fifty Fatal Cases of Heart Disease Occurring in Washington (D. C.) Hospitals During 1932, with Special Reference to Etiology, Race and Sex, *Pub. Health Rep.* **50** 1127, 1935.

6 Geiger, J. C., Sampson, J. J., Miller, R. C., and Gray, J. P. A Survey of Heart Disease Morbidity in San Francisco, *Am. Heart J.* **12** 137, 1936.

7 White, P. D., and Jones, T. D. Heart Disease and Disorders in New England, *Am. Heart J.* **3** 302, 1928.

8 Wyckoff, J., and Lingg, C. Statistical Studies Bearing on Problems of Classification of Heart Disease. II. Etiology in Organic Heart Disease, *Am. Heart J.* **1** 446, 1926.

9 Viko, L. E. Heart Disease in the Rocky Mountain Region, *Am. Heart J.* **6** 264, 1930.

its distribution in the United States) so swells the total of all types of vascular disease that hypertension is given a less important place in statistical studies based on relative, not actual, incidence is a question which must await further studies. Figures available from the registration area of the United States are of little value in solving the question, since they are based on anatomic rather than etiologic diagnoses. The need for revision of the classification of cardiac diseases in the "Manual of the International List of Causes of Death"¹⁰ has been pointed out by Hedley¹¹

ETIOLOGIC FACTORS IN THE SERIES OF CASES OF HYPERTENSION

An effort was made to ascertain the cause of the hypertension in each of the 289 cases of hypertensive cardiovascular disease. Little satisfaction was derived from this study because of the variation in the

TABLE 9—*Relative Incidence of Etiologic (?) Factors in Cases of Hypertensive Cardiovascular Disease*

Etiologic Factor	White Patients		Negro Patients		All Patients	
	No	Percentage	No	Percentage	No	Percentage
Arteriolar nephrosclerosis	18	78.2	229	86.1	247	85.5
Acute glomerulonephritis	0	0	3	1.1	3	1.0
Subacute glomerulonephritis	2	8.7	1	0.4	3	1.0
Chronic glomerulonephritis	0	0	20	7.5	20	6.9
Pyelonephritis	2	8.7	7	2.6	9	3.1
Congenital abnormalities	0	0	2	0.8	2	0.7
Thyrotoxicosis	0	0	1	0.4	1	0.3
Pituitary tumor	1	4.3	1	0.4	2	0.7
Eclampsia	0	0	2	0.8	2	0.7
Total no	23	99.9	266	100.1	289	99.9

terminology used by different pathologists during the ten year period. In the earlier part of the period covered by this report, many of the cases of hypertensive cardiovascular disease were listed, after histologic study of the kidneys, as instances of "chronic glomerular nephritis," while in more recent years in most of the cases the condition has been diagnosed as "nephrosclerosis" or "arteriolar sclerosis of the kidneys." Some of the older slides were reviewed in an attempt to reclassify the group, but in many cases it was impossible to decide between chronic glomerular nephritis and arteriosclerosis of the kidneys. One can hardly avoid the conclusion that any attempt to differentiate between the two, at least in the later stages, is pointless, either from a clinical or from a pathologic point of view. This is especially true if one admits the incompleteness of knowledge of the early phases of arteriosclerosis in the kidney and lack of knowledge of its cause. Table 9, indicating

10 Manual of the International List of Causes of Death, ed 4, United States Department of Commerce, Bureau of the Census, 1929

11 Hedley, O. F. Studies of Heart Disease Mortality, Public Health Bulletin 231, United States Treasury Department, Public Health Service, 1936

the relative incidence of the factors thought to be etiologic, in the light of present day ignorance of the matter, is presented for what it may be worth

Readers may wonder why many of the aforementioned groups are listed. Since all may be associated with clinical hypertension, with hypertrophy of the heart and with contracted kidneys, and may cause death in the same ways, there seems to be little reason for excluding them. Many cases of acute, subacute and chronic disease of the kidney, of pyelonephritis and of eclampsia in our autopsy records are not included in this study at all, since in these instances the criteria formulated in an earlier part of this paper were not met.

Nine of the 20 patients with chronic glomerulonephritis died of uremia. Their average age was 36 years, which is 8 years younger than the average age for the group with azotemia as a whole.

It is commonly taught that the subacute stage of glomerulonephritis is not associated with hypertension. In the 3 cases listed here the usual criteria for the histologic diagnosis of the subacute phase (most of the glomeruli showing proliferative changes and "epithelial crescents") were met, and at the same time the criteria used here for the diagnosis of hypertensive disease were satisfied.

In only 1 of the 2 cases of pituitary tumor associated with hypertension was the growth of the basophilic type. The other was a chromophobe adenoma. Whether the hypertension in the second case was a result of the tumor or whether the two conditions represented completely independent entities is a question.

ANNUAL AND SEASONAL VARIATIONS

Since several observers¹² have noted a pronounced difference in the blood pressure averages for large groups of supposedly normal persons, examined under the same circumstances, in different years, the cases of hypertensive disease were divided into groups according to years, and a chart was prepared showing the number of deaths from hypertension in each year as the percentages of all cardiovascular deaths and as the percentages of all autopsies. The results are shown in chart 1.

During the period covered by this study, deaths from hypertensive cardiovascular disease have tended to occur in definite cycles, no matter whether deaths from hypertension are compared with the total number of cardiovascular deaths (curve 1) or with the total number of autopsies (curve 2). Furthermore, a division of patients dying of hypertension

¹² Alvarez, W. C., Wulzen, R., and Mahoney, L. J. Blood Pressures in Fifteen Thousand University Freshmen, *Arch. Int. Med.* **32**: 17 (July) 1923.
Goepp, R. M. Blood Pressure as a Prognostic Factor, *Pennsylvania M. J.* **22**: 295, 1919.
Symonds, B. The Blood Pressure of Healthy Men and Women, *J. A. M. A.* **80**: 232 (Jan. 27) 1923.

into patients dying of uremia and heart failure combined (curve 3) and those dying of vascular accident (curve 5) shows in general the same configuration when expressed as percentages of the total autopsy group. Curve 4, showing deaths from nonhypertensive cardiovascular diseases expressed as percentages of all autopsies, also indicates variations from year to year.

As a test of the significance of the oscillations in these curves, the low point in 1928 and the peak in 1930 in curve 2 were taken. It was found that the difference in percentages in the two instances was statistically significant, and that chance could bring about the difference between peak and valley in less than 1 per cent of such investigations (as P is less than 1 per cent).¹³

A similar investigation of the oscillations in curves 1 and 3 shows that the difference between peak and valley is not beyond the limit of chance, but since the oscillations in curve 2 are statistically significant and since the other curves show in general the same variations and are based on the same cases, it seems reasonable to conclude that deaths from hypertensive cardiovascular disease in Charleston, S. C.,¹⁴ vary greatly from year to year and that the variation is not due to chance. The importance of this observation is apparent. If it could be confirmed by similar studies from other areas, or by an analysis by years of the number of new cases of hypertension seen in various clinics, it might serve as a clue to the factors in a disease which ranks among the chief causes of death in the United States and in the world.

Curve 4, showing nonhypertensive cardiovascular deaths, was also studied, the valley in 1934 being compared with the peak in 1935. This investigation showed that the difference between the two years is statistically significant. During 1935 the number of deaths from syphilitic cardiovascular disease was particularly increased.

13 In the formula $S = \frac{n_1 \bar{f}_1 (1 - \bar{f}_1) + n_2 \bar{f}_2 (1 - \bar{f}_2)}{(n_1 + n_2 - 2)} \times \frac{n_2 + n_1}{n_1 n_2}$, S is the standard deviation of the difference between the two percentages, expressed in decimals, n_1 is the total number of autopsies (176) performed in 1928, n_2 is the total number of autopsies (184) performed in 1930, \bar{f}_1 is the percentage of occurrences of deaths from hypertension in 1928, expressed as a decimal (0.102), and \bar{f}_2 is the corresponding figure for 1930, expressed as a decimal (0.217). The difference ($\bar{f}_2 - \bar{f}_1$), or 0.115, is divided by its standard deviation (0.038), and the quotient (3.03) is checked in the table of the distribution of "t."

14 Since there was no unusual concentration by the hospital staff on hypertensive disease during the period covered by these studies, it seems likely that the autopsy figures represent faithfully the trend in the total number of deaths. Furthermore, since the changes in the intern staff in the Roper Hospital are made in July of each year, the difference in the diligence of various intern groups in securing autopsies would be insignificant in statistics based on the calendar year.

Similarly, the total number of deaths from cardiovascular disease in general and from hypertensive cardiovascular disease in particular were subdivided according to the season of the year in which death occurred and were compared with the total number of autopsies performed in that season. Spring was considered as extending from March 1 through May, summer from June 1 through August, fall from September 1 through November and winter from December 1 through

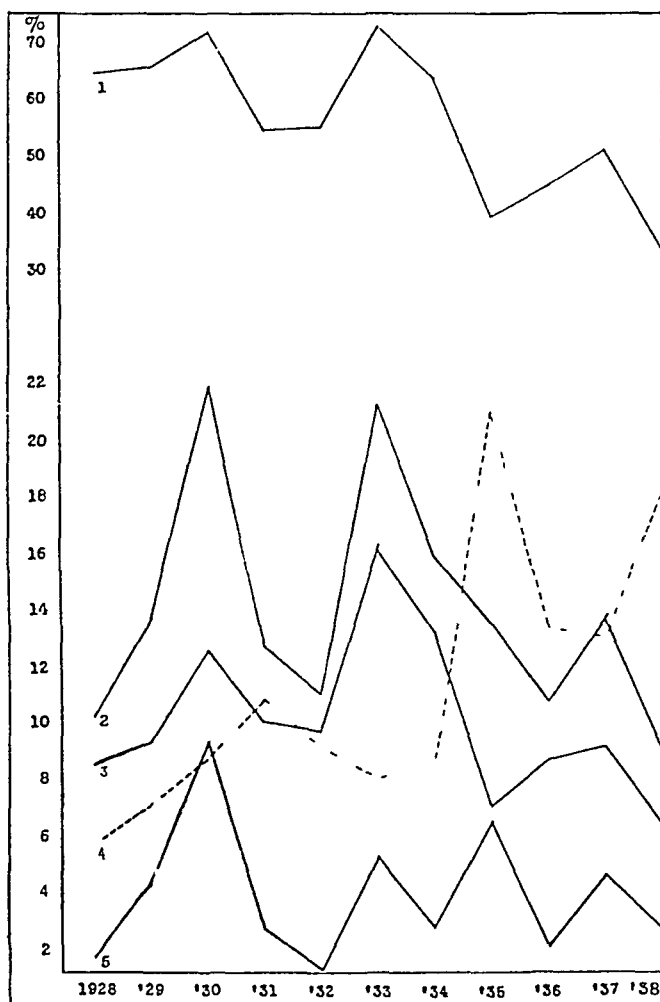


Chart 1—Annual variations in number of deaths from hypertensive cardiovascular disease

Curve 1 shows deaths from hypertension, expressed as percentages of all cardiovascular deaths, curve 2, deaths from hypertension, expressed as percentages of all autopsies, curve 3, deaths from uremia and heart failure due to hypertension, expressed as percentages of all autopsies, curve 4, deaths from all nonhypertensive cardiovascular diseases combined, expressed as percentages of all autopsies, and curve 5, deaths from vascular accidents due to hypertension, expressed as percentages of all autopsies

February The total number of autopsies performed in the spring months was 551 and included 69 cases in which death was from hypertensive disease, in the summer months there were 489 autopsies, with

65 cases of death from hypertensive disease, in the fall there were 461 autopsies, with 74 cases of death from hypertensive disease, and in the winter there were 505 autopsies, with 72 cases of death from hypertensive disease. The results of the analysis are illustrated graphically in chart 2. Here, curve 1 shows the number of deaths from hypertension, expressed as percentages of the total number of deaths from all cardiovascular diseases, curve 2 shows deaths from hypertension, expressed as percentages of the total number of autopsies, curve 3

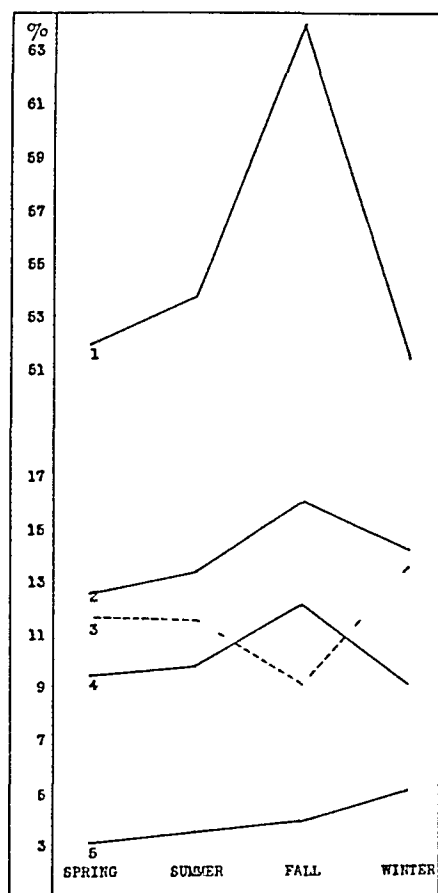


Chart 2—Seasonal variations in number of deaths from hypertensive cardiovascular disease

Curve 1, deaths from hypertension, expressed as percentages of all cardiovascular deaths, curve 2, deaths from hypertension, expressed as percentages of all autopsies, curve 3, deaths from all nonhypertensive cardiovascular diseases combined, expressed as percentages of all autopsies, curve 4, deaths from uremia and heart failure due to hypertension, expressed as percentages of all autopsies, and curve 5, deaths from vascular accidents due to hypertension, expressed as percentages of all autopsies

shows deaths from cardiovascular diseases not of hypertensive origin, expressed as percentages of all autopsies, curves 4 and 5 show a division of deaths from hypertension into those from uremia and heart

failure combined (curve 4) and those from vascular accidents (curve 5), in each instance expressed as percentages of all autopsies. The curves show a moderate rise in the number of deaths from hypertension in the fall, whereas the deaths from nonhypertensive cardiovascular disease were relatively more numerous in the winter months. Analysis of these figures shows that the variations are not beyond the margin of error. The fact that they are not does not mean that the variations are of no significance. Similar investigations from other sources would be of interest.

At present we are not prepared to draw conclusions from these graphs. An investigation of possibly related factors will be undertaken at an early date.

SUMMARY

In a series of 2,066 consecutive autopsies performed in Charleston, S. C., all cases in which death was from cardiovascular disease have been studied, using the clinical record, the autopsy protocol and, in many instances, the microscopic slides. These cases were then classified according to etiologic factors. Hypertensive cardiovascular disease was the etiologic factor in more than half the cases. When only cases of congestive heart failure were studied, it was noted that hypertensive cardiovascular disease again more than equaled all other etiologic types of heart disease combined. The incidence of hypertension was particularly high in the Negro race, and especially in the Negro male. While hypertension was common in the white race also, arteriosclerotic disease (without hypertension) was almost as frequently a cause of death. Syphilitic cardiovascular disease was seldom encountered in the white patients in this series.

Each etiologic group of cases of vascular disease was further divided according to the manner of death, and the average age at death was shown. In almost every category the Negro died earlier of vascular disease than did the white patient.

Coronary thrombosis, either with or without hypertension, was seldom encountered in the Negro, but in the white group it was common.

An attempt to classify the cases of hypertensive cardiovascular disease according to the factors bringing about hypertension met with little success.

The annual variations in deaths from hypertensive cardiovascular disease in this locality was studied, and the oscillations in the graph were shown to be greater than would be expected if chance alone were the important factor. This offers a lead for consideration in attempts to learn the cause of hypertensive disease.

Seasonal variations in deaths from hypertensive diseases were also shown, but these variations could be accounted for by chance error.

BLOOD "GUANIDINE"

FURTHER OBSERVATIONS

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In a recent article,¹ one of us (R H M) presented the results of estimations of the "guanidine" content of the blood of 800 patients with arterial hypertension. An increase in blood "guanidine" was found in 32 per cent of hypertensive persons with normal values for nonprotein nitrogen in the blood and in a higher percentage of patients with nitrogen retention. These observations have led directly to the following study, in which we have investigated the association in animals between high values for blood "guanidine" and the blood pressure and have also studied further the properties of the substance in the blood which with certain reagents gives a color like that of guanidine derivatives and which we have referred to as "guanidine."

Estimations of the blood pressure in these experiments were carried out by the palpatory method on carotid loops, a method permitting estimation only of the systolic pressure. Several different experimental procedures were employed, all caused renal insufficiency, some with and some without elevation in the blood pressure. In the first 3 experiments an arteriovenous fistula between the renal artery and the renal vein was formed and the remaining kidney removed at that time or later. This procedure in three instances produced marked elevation in blood pressure with renal insufficiency.

EXPERIMENTS

EXPERIMENT 1—A dog weighing 12.1 Kg. was used. The blood pressure from Nov. 9 to Nov. 14, 1938 varied from 80 to 120.

On November 14 an arteriovenous fistula of the left renal artery and vein was created. The following observations were made:

From the Hixon Laboratory of Medical Research, the University of Kansas School of Medicine.

1 Major, R. H. Blood "Guanidine" in Arterial Hypertension, *Arch. Int. Med.* 62: 946-948 (Dec.) 1938.

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
11/15/38	95	31	1.4	0.21	
11/16/38	110	25.7	1.4	0.21	
11/16/38 to	100 to				
11/25/38	125				
11/25/38	110	41	1.5	0.22	
11/26/38	175	71	3.8	0.24	Right kidney removed
11/27/38	185	127	11.3	0.58	
11/28/38	130	174	16.3	0.87	Severe vomiting
11/29/38	165	193	18.1	1.04	
11/30/38	165	259	22.2	1.46	
12/ 1/38	165	305	23.9	0.88	No urine voided since 11/25
12/ 2/38					Animal found dead

EXPERIMENT 2—A dog weighing 15.4 Kg. was used. An arteriovenous fistula of the right renal artery and vein was produced on Sept. 22, 1938. The blood pressure from September 22 to November 17 varied from 55 to 130. The following data were obtained:

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
10/17/38	65	23	1.4	0.2	
10/18/38	125	48	3.5	0.39	Left kidney removed
10/19/38	135				
10/20/38	90				
10/21/38	110				
10/22/38	150	142	16	1.13	
10/24/38	170	272	21.5	1.15	
10/25/38	140	321	27.7	1.96	
10/26/38	100	300	27.6	2.03	
10/27/38					Dog found dead

EXPERIMENT 3—A dog weighing 14.7 Kg. was used. The following data were obtained:

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
11/10/38	140				
11/11/38	135				
11/12/38	130				
11/13/38	145				
11/14/38	125	32	1.4	0.18	

An arteriovenous fistula was made in the left renal artery and vein. The right kidney was removed. The following additional data were obtained:

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
11/15/38	170	88	5.6	0.6	
11/16/38	170	157	9.6	1.4	
11/17/38	190	250	12.1	1.23	
11/18/38					Dog found dead

In summary, the results of these 3 experiments show that in each instance there was a marked rise in systolic blood pressure accompanied by retention of nitrogen and a great increase in the "guanidine" content of the blood.

In the following experiment one kidney was removed and a Goldblatt clamp placed on the vein of the other kidney. The protocol is as follows:

EXPERIMENT 4—A dog weighing 11.65 Kg was used. The following data were obtained

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
12/12/38	115				
12/13/38	80	22.8	1.2	0.4	Right nephrectomy, clamp on left renal vein
12/14/38	70	70	3.2	0.5	
12/15/38	95	147	6	1.143	
12/16/38					Dog found dead

In this experiment there was no increase in the systolic blood pressure, although there were marked retention of nitrogen and a great increase in the "guanidine" content of the blood

In the 2 following experiments both kidneys were removed and the effect upon the blood pressure and the "guanidine" content of the blood noted

EXPERIMENT 5—A dog weighing 12.7 Kg was used. The left kidney was removed Dec 20, 1938

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
12/30/38	80				
12/31/38	75				
1/ 3/39	100	42	2.1	0.19	Right kidney removed
1/ 4/39	70	77.9	3.6	0.87	
1/ 5/39	90	150	9.6	0.92	
1/ 6/39	130	194	12	0.82	
1/ 7/39	135	220	20	1.34	
1/ 9/39	135	289	25	1.54	
1/10/39	90	306	26	1.36	
1/11/39	110	325	27.7	2.16	
1/12/39	125	375	32.7	2.08	
1/13/39					Dog died

EXPERIMENT 6—A dog weighing 9.8 Kg was used. The dog was operated on April 30, 1936, at which time both renal arteries were partially constricted with Goldblatt clamps. The blood pressure was elevated from April 30 to July 17, varying from 190 to 270 millimeters of mercury. The range of blood pressure from December 8 until Dec 20, 1938, was 150 to 180 millimeters of mercury. The following data were obtained

Date	Blood Pressure	Nonprotein Nitrogen	Creatinine	"Guanidine"	Comment
12/20/38	160	26	1.3	0.54	Left kidney removed
12/21/38	110	22	1.3	0.67	
12/22/38	160	22	1.3	0.24	
12/23/38	150	18.5	1.2	0.174	
12/25/38	160				
12/30/38	170				
12/31/38	195	21	1.2	0.197	
1/ 3/39	165	26	1.6	0.183	
1/ 4/39	110	76.9	2.9	0.87	Right kidney removed
1/ 5/39	115	146	6.4	0.87	
1/ 6/39					Dog died

Experiment 6 was especially interesting, since the animal had elevation of blood pressure for more than two years and showed definite hypertension at the beginning of the experiment. After removal of both kidneys, although the "guanidine" content of the blood increased rapidly, the blood pressure actually fell lower than it had been in two years.

In experiments 4 and 5 there was a marked increase in the "guanidine" content of the blood without any elevation in blood pressure.

We have also attempted to establish the identity of the substance in the blood which we have provisionally designated as "guanidine." This problem was studied by producing severe "uranium nephritis" with renal insufficiency in dogs. After the values for creatinine and "guanidine" had become very high, the dogs were killed and the entire amount of blood was removed. In all, 20 dogs were employed, approximately 25 liters of blood was obtained, from which 150 liters of filtrate was studied. The nephritis was produced by giving the animals uranium nitrate in doses of 20 mg per kilogram of body weight. The dogs when killed showed values for blood creatinine varying from 15 to 16 mg per hundred cubic centimeters.

In an attempt to isolate the "guanidine," we have employed tungstic acid filtrates of blood from dogs in the last stages of "uranium nephritis." These filtrates were extracted with Lloyd's reagent and an eluate prepared from it, by means of a saturated barium hydroxide solution. We have found that "guanidine" is precipitated from these eluates by phosphotungstic acid or by trinitrophenol. The precipitation is more complete with trinitrophenol if potassium chloride is also added. Thus far we have been unable to separate it from creatinine.

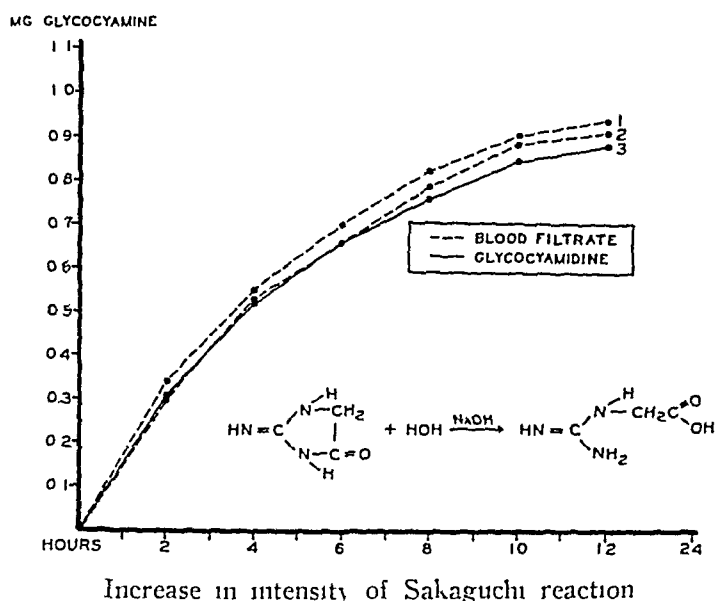
The similarity of the color given by these more concentrated solutions with the ferricyanide-nitroprusside reagent to that given by a solution of glycohydrazide is striking. In fact, it is difficult to compare this color in the colorimeter with that of any of the guanidine bases or their derivatives (such as arginine, glycohydrazine or creatinine) except glycohydrazide. This similarity in color value is present with all concentrations.

We found in previous work that norit (a prepared charcoal) and Lloyd's reagent (a specially prepared siliceous earth) would absorb simple guanidine bases from the aqueous solutions and that these bases are readily released from norit by means of acid alcohol, an average of 80 to 90 per cent of guanidine bases being released after this treatment. We have also found that the simple guanidine bases are released from Lloyd's reagent by means of barium hydroxide solution only to the extent of approximately 30 per cent of the absorbed amount. We have therefore compared the amount released from norit and Lloyd's reagent extracts of the tungstic acid filtrates of dog blood, acid alcohol

being employed to produce release from norit and barium hydroxide to produce release from Lloyd's reagent (table)

Comparison of the Color Values of Norit and Lloyd's Reagent Extract with Use of the Alkaline Nitroprusside Ferricyanide Reagent (Methylguanidine Employed as Standard)

No	Guanidine Bases with Lloyd's Reagent Extract, Mg per 100 Cc	Guanidine Bases with Norit Extract, Mg per 100 Cc	Comment
1	0.81	0.84	Normal dog blood
2	0.88	0.74	Normal dog blood
3	1.11	2.27	2 mg methylguanidine added
4	1.30	2.24	2 mg guanidine added
5	4.18	4.32	Uranium nephritis (N P N 300)
6	3.95	3.48	Uranium nephritis (N P N 225)



If the increase in color in experiments 5 and 6 was due to simple guanidine bases, the value for the Lloyd's reagent extracts should have been approximately 2.1 mg instead of 4.18 and 3.95 mg. This observation is strong evidence against this compound being a simple guanidine base.

We have also studied the question whether this increase in color, which we have designated as due to increased "guanidine," is due to a substance normally present in dog blood. Normal dog blood before treatment with arginase gives an appreciable color varying from that indicating 0.4 mg to that indicating 0.8 mg of guanidine per hundred cubic centimeters. The major part of this color is removed by treatment with arginase. After such treatment there remains a small amount of color, representing a value of 0.1 mg to 0.2 mg of methylguanidine per hundred cubic centimeters. This observation, which has

been repeated many times, indicates that most of the color attributed to the presence of "guanidine" in dog blood is really due to arginine. The substance present in the blood of dogs with "chronic nephritis" is not reduced in amount by treatment with arginase, which would seem good reason to believe that it is not arginine.

We have made studies regarding the behavior of this substance toward Sakaguchi's reagent. This reagent, as is well known, is apparently specific for guanidine compounds containing one group substitution. Normal dog blood with norit extract or Lloyd's reagent gives a well marked Sakaguchi reaction. After treatment of the blood with arginase, however, the color produced is reduced approximately 90 per cent. The intensity of Sakaguchi's reaction was not increased in our experiments after the dogs showed marked renal insufficiency. The guanidine-like substance which is increased in the blood of these dogs with renal insufficiency does not give a positive Sakaguchi reaction.

We have found that the substance referred to as "guanidine" is precipitated by phosphotungstic acid and trinitrophenol. Complete separation from creatinine has not been achieved. We have found that solutions of this substance obtained from the blood in the presence of renal insufficiency when made alkaline and allowed to stand show a gradual increase in intensity of the Sakaguchi reaction. The increase in color is at a rate similar to that produced in a solution of glyco-cyamidine similarly treated (see chart). These observations indicate that the substance is a guanidine derivative of an anhydride type and that under alkaline treatment the guanidine ring opens and the resulting compound gives a Sakaguchi reaction.

CONCLUSIONS

1. The increase in "guanidine" in the blood in experimental renal insufficiency occurs both with and without accompanying hypertension.

2. The compound which we have designated as "guanidine" is apparently a guanidine derivative of an anhydride type and may be glyco-cyamidine.

MULTIPLE MYELOMA

HELMUTH ULRICH, M D

BOSTON

The problem of the cytologic origin and relation of multiple myeloma has been one of the puzzles of medicine ever since Macintyre¹ reported the first case nearly a hundred years ago. There are indications that the problem is approaching a solution. It is hoped that the following report of a case, particularly the correlation of its many interesting features with those reported in the literature, may contribute to a better understanding of the disease.

REPORT OF A CASE

A W R, a chemist aged 55, was admitted in October 1934 to the Massachusetts Memorial Hospitals, with weakness as the most prominent symptom. The historical data included fracture of the right tibia as a result of a fall in 1923, paracentesis of the left ear drum in 1928, "septic" throat in 1930 and many migrainous headaches, which had become much less severe in recent years.

About six months before entering the hospital he had experienced a "sensation of adhesions in the right side of the chest." Shortness of breath, progressive fatigability and a hacking cough came on three months later. The cough interfered with sleep. The muscles of the neck felt stiff, headache was produced by stretching either side of the neck. Sore mouth, loss of appetite, nausea, slight recurrent attacks of diarrhea and flatulence developed. A month later he noticed a firm, somewhat tender tumor in the left testicle. A persistent nasal discharge appeared, with intermittent pain and discomfort in the antrums, especially the left.

The patient was well developed and slightly obese. The greatest weight, several years ago, had been 210 pounds (95.2 Kg), at the time of admission to the hospital he weighed 188 pounds (85.3 Kg). The skin had a yellowish pallor. The tongue was coated and the breath foul. There were shallow ulcerations of the gums and many dental fillings. Moist rales were heard throughout the lungs, especially in the upper lobe of the right. The heart was normal. The pulse rate was 82, the blood pressure 148 systolic and 84 diastolic and the temperature 99 F. The liver, spleen and kidneys were not felt. There were several small firm nodules in the left testicle.

The urine contained a large amount of albumin, a few leukocytes and erythrocytes and a number of hyaline, finely and coarsely granular and epithelial casts. Bence Jones protein was not found. Examination of the blood revealed marked anemia of the hypochromic type. The Wassermann, the Kahn and the Hinton reactions were negative. The icteric index was 7, the bleeding time six minutes, the clotting time (Lee and White) nine minutes and clot retraction normal. Other

From the Evans Memorial of the Massachusetts Memorial Hospitals and the Boston University School of Medicine.

1 Macintyre, W. A Case of Mollities and Fragilitas Ossium, Accompanied with Urine Strongly Charged with Animal Matter, *Med-Chir Tr* 33:211, 1850.

hematologic data are shown in the table Occult blood was found in the feces The Takata-Ara reaction was positive Two Aschheim-Zondek tests gave negative results

An electrocardiogram was normal The basal metabolic rate was +5 per cent Roentgenograms revealed an old fracture of the lower part of the right tibia, with hypertrophic changes about the ankle The skeleton showed nothing suggesting multiple myeloma (In a film of the skull made at the time of necropsy a few small "punched-out" areas of rarefaction could be seen) Films of the scrotum showed a small dense shadow suggesting calcareous deposition in a teratoma (This finding led to the performance of the previously mentioned Aschheim-Zondek tests)

The left testicle was removed for examination It contained several small tumors made up chiefly of cells having the appearance of atypical plasma cells

Hematologic Data

	Date (1934)											
	10/30	11/1	11/6	11/8	11/9	11/13	11/17	11/26	11/28	11/30	12/3	12/5
Red cells (millions)	2 15		1 57	1 35		1 55	2 33	2 63	2 76	2 41	1 8	
Hemoglobin, %	39		35	30		33	45	50	50	47	35	
Leukocytes (thousands)	11 4		10	7 3		9 8		9 9	7 3	6 5	6 4	
Neutrophils	12		40	48		72	48	50	60	54	67	
Lymphocytes	38		20	13		28	35	39	30	40	26	
Myelocytes and myeloblasts	5		19	12		10	9	6	3	2	5	
"Plasma cells"	8		5	10		2	5	3	1	1	0	
Doubtful forms			10	12								Few
Serum protein, %		10 6		13							14 9	
Serum albumin, %		2 2		3							3 1	
Serum globulin, %		8 4		10							11 8	
Serum calcium, mg per 100 cc		9 9			10		9 4					
Serum phosphorus, mg per 100 cc		4 2			7 5							
Nonprotein nitrogen, mg per 100 cc										101	185	240

The cytoplasm was basophilic in many of them, the nucleus was eccentric in some, and a perinuclear *Hof* was present in a few The chromatin, however, only rarely showed a tendency to radial arrangement Some of the cells appeared definitely to be young myeloid cells (stem cells, lymphoidocytes and premyelocytes), with their characteristic nucleoli Several mitoses were seen

The patient was transferred to the Collis P Huntington Memorial Hospital for roentgen treatment During his stay there his symptoms gradually increased in severity The weakness became extreme, nausea was constant, and all food caused vomiting Bleeding from the gums and nose became troublesome Many spirochetes and fusiform bacilli were found in smears from the gums The temperature rose to 104 F At no time was pain of importance, except for occasional headache The urine persistently contained large amounts of albumin, a variable number of casts and traces of pus and blood During the last few days of life there was marked oliguria Repeated tests for Bence Jones protein gave negative results

Treatment consisted of five blood transfusions of 300 to 500 cc each and small doses of high voltage roentgen radiation and radium, applied to the thighs, pelvis and sternum. There was no evidence that these measures had any beneficial results, except for a temporary increase in the number of red blood cells after each transfusion. The patient finally became irrational and comatose and died five weeks after admission to the hospital, four months after the onset of symptoms.

Necropsy was performed by Dr. Shields Warren. There follows an abstract of his report.

The lymph nodes were not palpable. The liver extended 5 cm below the costal margin. The lungs contained a few small discrete dark red or grayish foci of bronchopneumonia. The spleen weighed 380 Gm and the liver 2,120 Gm. The capsule of the kidneys stripped readily from a smooth grayish white surface. The renal medulla and cortex were not clearly demarcated. Both kidneys were pale, the glomeruli were not visible. The left testicle had been removed, the right was infiltrated in its lower anterior third with a firm grayish yellow tumor, which faded indefinitely into the surrounding testicular substance and penetrated slightly the overlying tunica. The femur, vertebrae, ribs and sternum contained pale yellow or yellowish red marrow of uniform texture. Bony trabeculation was normal. The skull could be sawed with remarkable ease, but there was no other definite evidence of softening. The cranial bone was only 0.2 to 0.4 cm thick, with almost complete absence of diploe. When the removed portion of the skull was held up to the light, reddish areas suggesting hemopoiesis were seen. They corresponded roughly to the rarefied areas seen in roentgenograms taken post mortem.

Microscopic Examination—Spleen. The normal structure was obliterated. The follicles had almost entirely disappeared, and the sinusoidal structure was seen in only a few parts. Large numbers of immature but not clearly identified blood cells filled the sinuses and reticulum. Most of these cells showed basophilic, slightly granular cytoplasm, with a central or eccentric vesicular nucleus, often with a single, prominent nucleolus. Mitotic figures were relatively rare.

Kidney. The majority of the glomeruli were swollen and edematous, and occasionally one was adherent to the capsule. There were one or two sclerosed glomeruli. The tubules were separated by a fairly uniform increase in the fibrous tissue of the stroma. The epithelium, especially of the proximal convoluted tubules, showed slight to marked albuminous degeneration. Some of the tubules contained polymorphonuclear leukocytes and others hyaline casts. Clusters of immature blood cells were present between the tubules. They were for the most part of the granulocytic series, though a few lymphocytes and plasma cells were seen. Neutrophilic and eosinophilic myelocytes, premyelocytes and cells similar to those seen in the spleen and testis could be definitely identified. Mitoses were frequent.

Testis. There was diffuse cellular infiltration of interstitial tissue, varying from wide separation of tubules to the presence of only scattered cells (figs 1 and 2). The infiltrating cells were fairly uniform and discrete, there was no supporting stroma or increased vascularity. The cells ranged from 5 to 10 microns in diameter, most of them being about 8 microns. They were rounded or polyhedral, with a tendency to mosaic patterning. The cytoplasm was usually basophilic, opaque and finely granular, with occasionally a clearer crescent adjacent to the eccentric nucleus. The nucleus was round or oval, with clearcut blocklike distribution of chromatin and a well marked nuclear membrane. Among these cells were rare somewhat larger ones with a large vesicular nucleus and scattered neutrophilic and eosinophilic granules. With Unna's stain many of the smaller

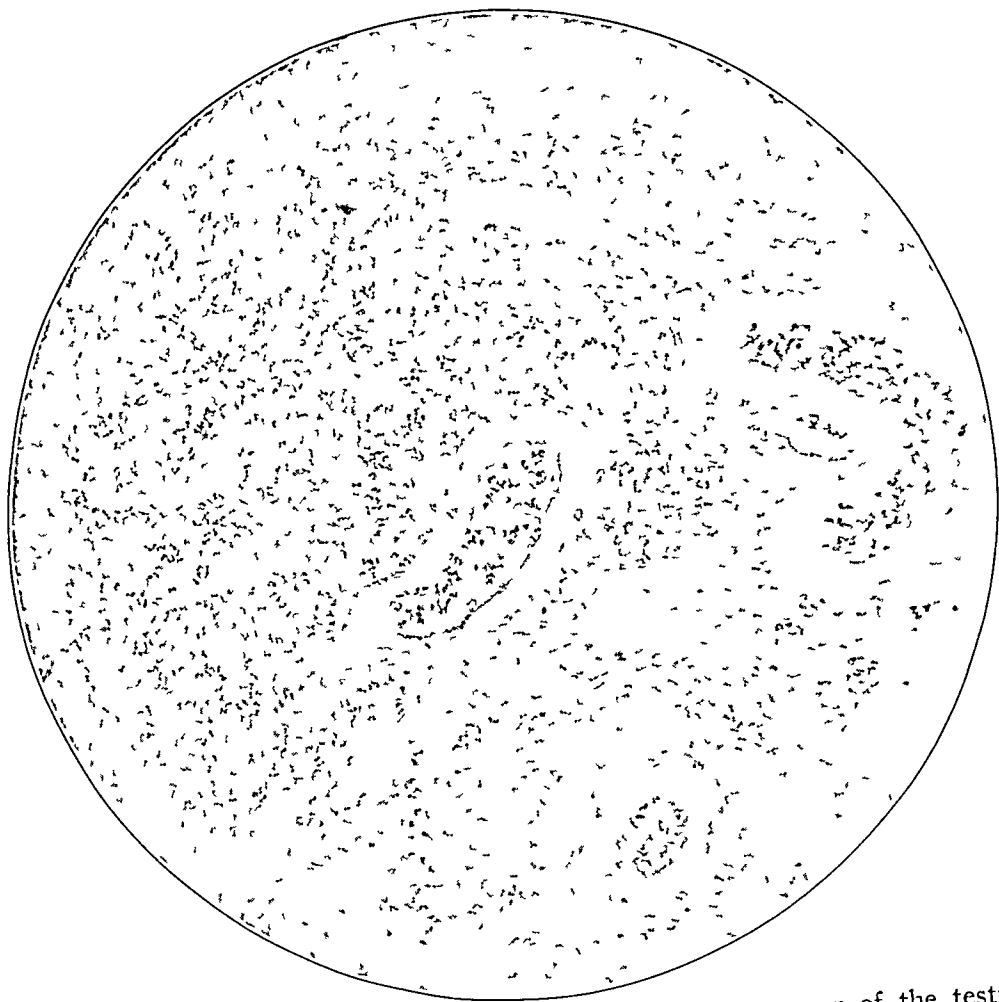


Fig 1—Low magnification of section of myelomatous tumor of the testis

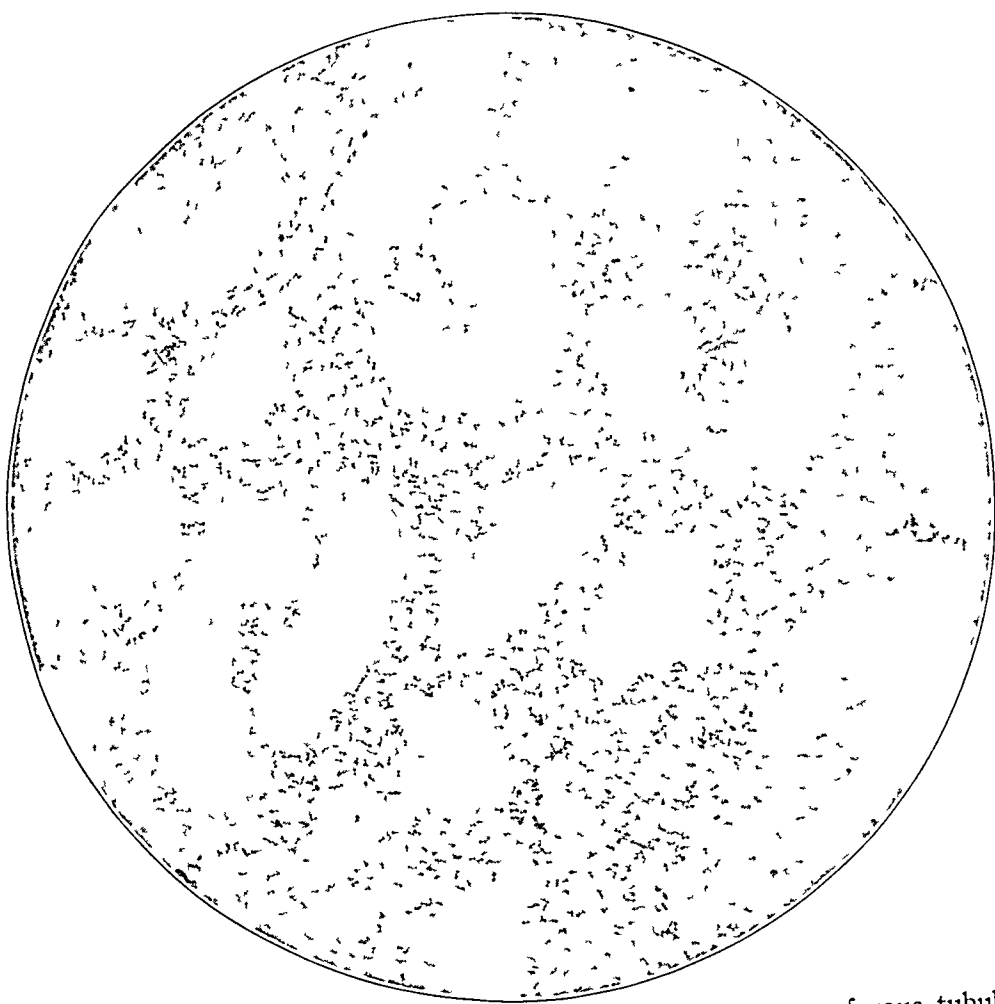


Fig 2—Invasion of myeloma cells of stroma between seminiferous tubules

cells showed a rose cytoplasm. This picture was identical with that seen in the surgically removed testis (fig 3).

Bone Marrow A portion of the marrow was fatty, the remainder was completely filled by fairly uniform masses of cells. Most of the cells were of immature type, with a large, somewhat vesicular type of nucleus and a prominent

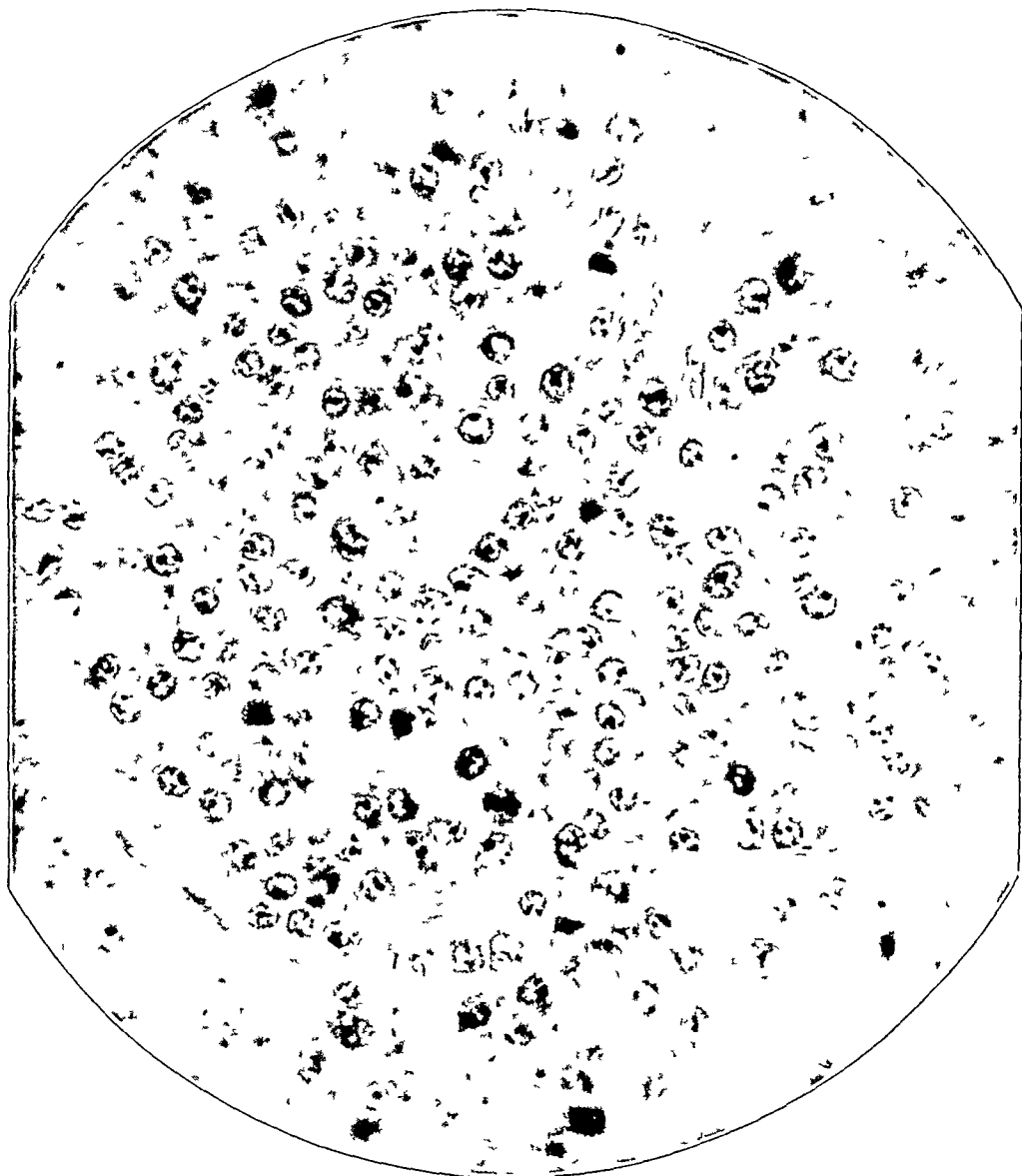


Fig 3—High magnification of testicular tumor, showing mitoses

nucleolus. The cytoplasm was scanty and somewhat basophilic. No granules were seen. In some portions there were neutrophilic and eosinophilic myelocytes. The reticuloendothelial cells were not remarkable.

Dr Warren wrote in his summary: "This case is most obscure, and the final diagnosis is still somewhat uncertain." He expressed the belief that aleukemic myeloblastic leukemia had to be considered. The identity of the abnormal cells was not, he stated, established with certainty, although subsequent study convinced him that they were plasma cells.

I had assumed that the cells found ante mortem in the peripheral blood of this patient were atypical plasma cells such as had been reported in a number of cases of multiple myeloma by other authors. A few myelocytes and myeloblasts also were present in the blood, and these too had been observed in several reported cases of myeloma (fig 4). Because of the uncertain status of the tumor cells,

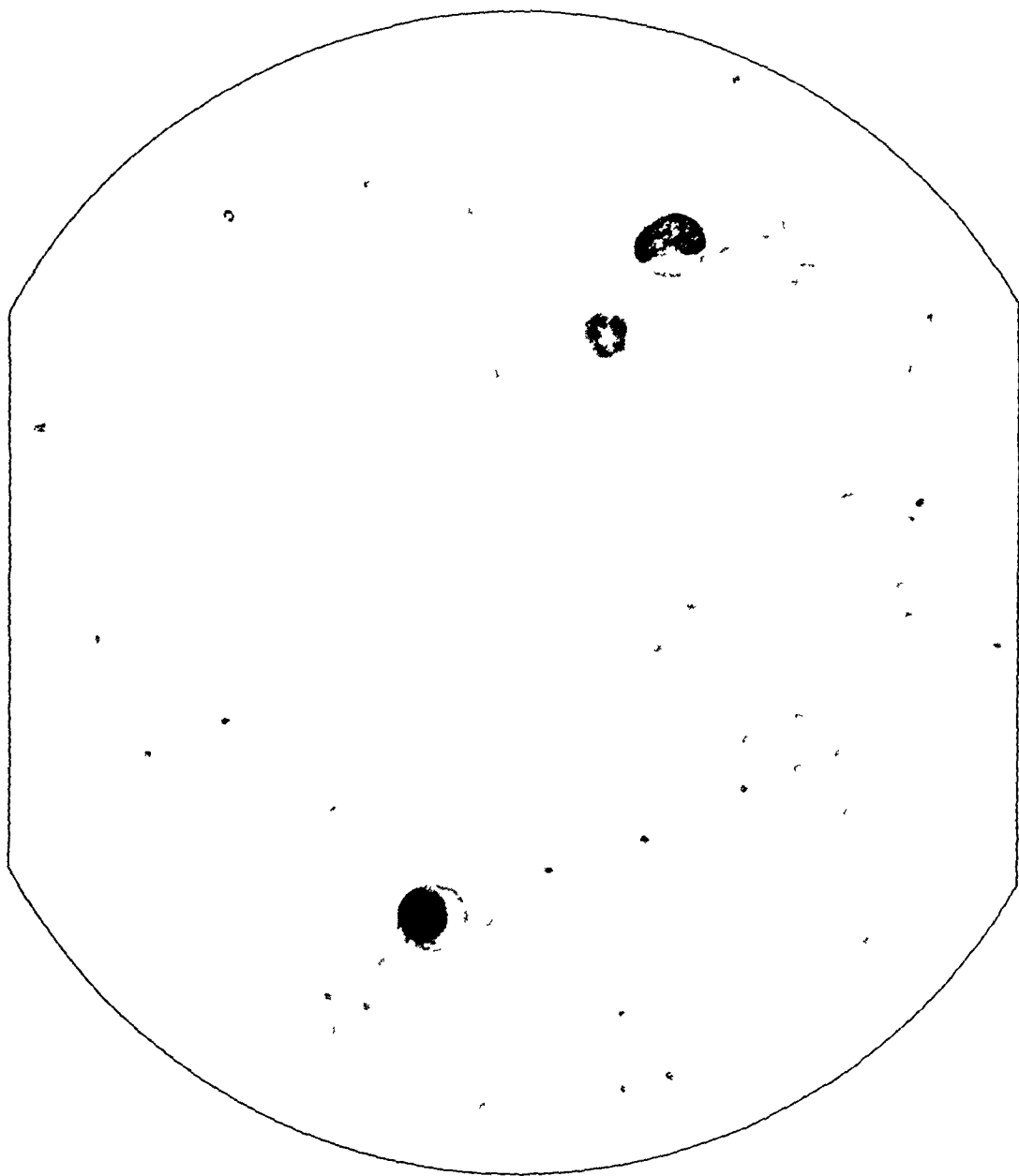


Fig 4—Blood film, showing neutrophilic myelocyte (top) and myeloma cell (below)

sections of the testicular tumors were submitted by Dr Warren to a number of pathologists² for their opinions. There was general agreement that the neoplastic cells, like those observed in the blood, were plasma cells of an atypical form. The

² Drs C F Branch, F Stewart, C F Geschickter, F Parker, R H Jaffé, Hal Downey, William Bloom and R P Custer

diagnosis of multiple myeloma of the so-called plasma cell type appeared, therefore, to be justified

Although Wallgren³ has pointed out that different authors have used different criteria for the diagnosis of multiple myeloma, the present generally held conception is of a multiple tumor of bone marrow, or a diffuse hyperplasia, consisting usually of cells resembling plasma cells. Geschickter and Copeland⁴ gave six cardinal diagnostic clinical signs of multiple myeloma, usually present "collectively or in pairs or triads in any individual case" (1) multiple tumor of the skeletal trunk in a person who is more than 35 years old, (2) pathologic fracture of a rib, (3) Bence Jones proteinuria, (4) lumbar backache and signs of early paraplegia, (5) otherwise unexplained anemia, and (6) chronic nephritis with azotemia and low blood pressure. Later, however, Geschickter⁵ reported a case of multiple myeloma that presented none of these features. In my case only points 5 and 6 were fully satisfied. Point 1 was partially fulfilled, but the site of demonstrable skeletal tumors was the skull rather than the trunk.

TRAUMA

The patient gave a history of a fall and fracture of the right tibia eleven years before the clinical onset of myeloma. It seems unreasonable to suppose that there was an etiologic relation between them. The interval was too long, and the incidence of trauma of some sort in persons of middle age is high. Geschickter and Copeland⁴ found a history of trauma in 20 per cent of reported cases, but they expressed doubt as to its significance and stated that "there is no evidence at hand to substantiate preceding fracture of healthy bone as an etiologic factor." Nevertheless, one is bound to be impressed by the frequency with which trauma has been reported as initiating the symptoms in patients who had previously felt well. I doubt that it can be eliminated entirely as a causative factor, although in most cases the injury undoubtedly occurred after the disease had already begun. It is of interest to refer to a medicolegal case⁶ in which damages were awarded on the basis of the jury's verdict that myeloma developed as a result of an injury and was the cause of death eight months later.

³ Wallgren, A. Untersuchungen über die Myelomkrankheit, *Upsala läkareförh* **25** 113, 1920.

⁴ Geschickter, C. F., and Copeland, M. M. Multiple Myeloma, *Arch Surg* **16** 807 (April) 1928.

⁵ Geschickter, C. F. Multiple Myeloma as a Single Lesion, *Ann Surg* **92** 425, 1930.

⁶ Myeloma Attributed to Trauma, *Medicolegal Reports, J. A. M. A* **97** 415 (Aug. 8) 1931.

PAIN

In most of the published reports pain was the outstanding symptom of multiple myeloma. In the present instance pain that could be ascribed directly to the myeloma was absent. The patient complained at times of headache, to which he had been subject in greater degree before (for many years) than after the myeloma appeared, also, he had slight pain in the antrum of Highmore, which was believed to have been the result of infection and congestion of the sinuses and not a direct result of the major disease.

Pain is apparently less likely to be a prominent symptom when, as in this case, there is diffuse involvement of the marrow,⁷ or when the tumor is situated in tissue without skeletal involvement.⁸

A compilation of the incidence of pain, of clinically recognized tumor, of roentgen evidence of the disease and of Bence Jones proteinuria in 259 cases of multiple myeloma, selected because the histories were given with sufficient clarity regarding each of these items, shows that absence of pain was rare (4.6 per cent), clinical recognition of the tumor was much less frequent (36.7 per cent) than roentgen evidence of it (96.9 per cent), and Bence Jones protein could not be detected in a substantial proportion of the cases (38.2 per cent).

BENCE JONES PROTEINURIA AND RENAL LESION

In 1930 Perla and Hutner⁹ reported a case which, according to Bell,¹⁰ "is the only case in the literature of proved renal insufficiency in a myeloma without Bence-Jones proteinuria." The case presented here appears to be another, a renal lesion was indicated by gross albuminuria, cylindruria and an ultimate increase of the nonprotein nitrogen content of the blood to 240 mg.

Marked albuminuria without Bence Jones proteinuria appears to be unusual in cases of multiple myeloma. Magnus-Levy¹¹ expressed the

7 (a) Diffuse Multiple Myeloma, Cabot Case 21082, *New England J Med* **212** 353, 1935. (b) Foord, A. G., and Randall, L. Hyperproteinemia, Auto-hemagglutination and Renal Insufficiency in Multiple Myeloma, *Am J Clin Path* **5** 532, 1935.

8 (a) New, G. B., and Harper, F. R. Plasma Cell Myeloma of the Pharynx and Cervical Region Without Skeletal Involvement, *Arch Otolaryng* **16** 50 (July) 1932. (b) Jackson, H., Jr., Parker, F., Jr., and Bethea, J. M. Studies of Diseases of the Lymphoid and Myeloid Tissues. II. Plasmacytomas and Their Relation to Multiple Myelomas, *Am J M Sc* **181** 169, 1931.

9 Perla, D., and Hutner, L. Nephrosis in Multiple Myeloma, *Am J Path* **6** 285, 1930.

10 Bell, E. T. Renal Lesions Associated with Multiple Myeloma, *Am J Path* **9** 393, 1933.

11 Magnus-Levy, A. Ueber die Myelomkrankheit. III. Vom Stoffwechsel, die Bence-Jones Proteinurie, *Ztschr f klin Med* **119** 307, 1932.

view that massive albuminuria in this disease is due chiefly to the presence of Bence Jones protein, and that reports of its absence when large amounts of albumin are present in the urine were erroneous. He claimed that the Bence Jones bodies were overlooked, owing to the fact that they may be insoluble under certain conditions in boiling urine, especially when present in large amounts. Bloch,¹² Hopkins and Savory¹³ and Berglund and Medes¹⁴ called attention to the difficulties that may be encountered in testing for these proteins and stated that their solubility at the boiling point depends to an important degree on the relation of salts to acids in the solution. The investigations of Bayne-Jones and Wilson,¹⁵ supported by Robinson's¹⁶ studies, indicated that "Bence-Jones protein is not a single substance, but a group of similar, but not identical proteins," and that this complexity may have a bearing on the difficulties of determining its presence under certain circumstances. Magnus-Levy¹⁷ therefore estimated the incidence of Bence Jones proteinuria with multiple myeloma to be about 80 per cent rather than 65 per cent, as given by Geschickter and Copeland¹⁸.

In the present case tests for Bence Jones protein gave persistently negative results. Furthermore, the microscopic examination of the kidneys (fig. 5) revealed nothing resembling the histologic changes which Forbus and his associates¹⁹ regarded as characteristic of renal damage resulting from excretion of Bence Jones protein.²⁰ Feller and Fowler²¹

12 Bloch. Ein Beitrag zur Klinik und Diagnose des multiplen Myeloms, *Folia haemat* **26** 119, 1921

13 Hopkins, F. G., and Savory, H. A Study of Bence-Jones Protein, and of the Metabolism in Three Cases of Bence-Jones Proteinuria, *J. Physiol.* **42** 189, 1911

14 Berglund, H., and Medes, G. The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935

15 Bayne-Jones, S., and Wilson, D. W. Immunological Reactions of Bence-Jones Proteins. I. Differences Between Bence-Jones Proteins and Human Serum Proteins, *Bull. Johns Hopkins Hosp.* **33** 37, 1922

16 Robinson, S. H. G. An Investigation of the Antigenic Properties of Four Specimens of Bence-Jones Protein Obtained from Cases of Myelomatosis, *Brit. J. Exper. Path.* **8** 454, 1927

17 Magnus-Levy, A. Ueber die Myelomkrankheit. VI. Beitrage zur Klinik und Pathologie, *Ztschr. f. klin. Med.* **121** 533, 1932

18 Geschickter, C. F., and Copeland, M. M. Tumors of Bone, ed. 2, New York, American Journal of Cancer, 1936

19 Forbus, W. D., Perlzweig, W. A., Parfentjev, I. A., and Burwell, J. C., Jr. Bence-Jones Protein Excretion and Its Effects on the Kidney, *Bull. Johns Hopkins Hosp.* **57** 47, 1935

20 Dr. Forbus examined a section of the kidney and agreed "that the picture is not that which I have described in cases of Bence Jones proteinuria."

21 Feller, A. E., and Fowler, W. M. Hyperproteinemia in Multiple Myeloma, *J. Lab. & Clin. Med.* **23** 369, 1938

and Barfield-Carter²² reported cases of marked albuminuria, but Bence Jones protein was never detected

Thannhauser and Krauss²³ and subsequent authors, notably Peila and Hutner,⁹ expressed the belief that the nephropathy of multiple myeloma is a form of nephrosis. Ehrich,²⁴ however, came to the conclusion that it is a question not of epithelial degeneration leading to tubular destruction (nephrosis) but of plugging of the tubules with casts

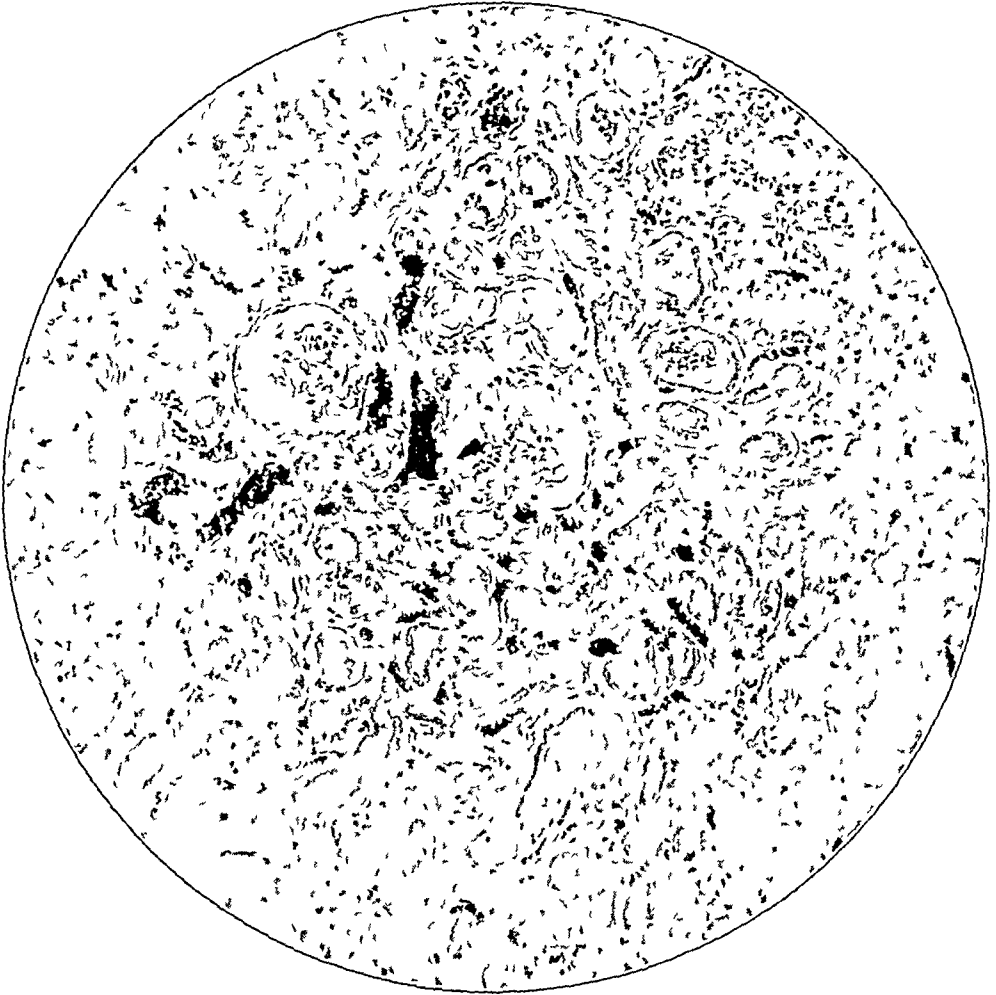


Fig 5—Section of kidney, showing hyaline casts

of Bence Jones protein and subsequent hydronephrotic atrophy. Bell¹⁰ stated

The only direct effect of multiple myeloma on the kidneys is due to the formation of tubular casts of Bence-Jones protein that obstruct the tubules

22 Barfield-Carter, M. Multiple Myeloma and Associated Renal Lesions, *Am J Roentgenol* **36** 830, 1936

23 Thannhauser, S. J., and Krauss, E. Ueber eine degenerative Erkrankung der Harnkanälchen (Nephrose) bei Bence-Jones'scher Albuminurie, *Deutsches Arch f klin Med* **133** 183, 1920

24 Ehrich, W. Die Nierenerkrankung bei Bence-Jonesscher Proteinurie, *Ztschr f klin Med* **121** 396, 1932

Casts were not found in the 2 cases of his series in which no Bence Jones protein was excreted. This explanation was not accepted as wholly satisfactory by Buschke,²⁵ and Randerath²⁶ concluded that his experiments contradicted the observations of Ehrlich and justified the inclusion of the renal changes among the nephroses.

Bell¹⁰ wrote that "none of the authors mentions hematuria in a case of multiple myeloma." That is true in regard to gross hematuria, but there have been several reports²⁷ of the observation of blood by microscopic examination, and in Lewis'²⁸ case the hematuria was sufficiently profuse for the patient himself to be aware of it. A few red disks were present in a number of the urinary specimens voided by my patient.

HYPERPROTEINEMIA

An increase of the total protein in the blood plasma or serum in cases of multiple myeloma has been reported by a number of observers. Schumacher, Williams and Coltrin²⁹ reported the huge amount of 23.29 per cent. That a high serum protein level is a valuable diagnostic finding is substantiated by Jeghers and Selesnick³⁰ who reported that of 13 cases of hyperproteinemia observed in recent years at the Boston City Hospital 7 were instances of multiple myeloma, in the others the protein

25 Buschke, F. Uramie bei Bence-Jonesscher Albuminurie, *Klin Wchnschr* **11** 408, 1932.

26 Randerath, E. Pathologisch-anatomische und experimentelle Untersuchungen zur Frage der Nierenveränderungen bei Bence-Jonesscher Proteinurie, *Ztschr f klin Med* **127** 527, 1934.

27 (a) Wintrobe, M. M., and Buell, M. V. Hyperproteinemia Associated with Multiple Myeloma, *Bull Johns Hopkins Hosp* **52** 156, 1933. (b) Sweigert, C. F. Multiple Myeloma with Hyperproteinemia, *Am J M Sc* **190** 245, 1935. (c) Bannick, E. G., and Greene, C. H. Renal Insufficiency Associated with Bence-Jones Proteinuria. Report of Thirteen Cases with Note on Changes in Serum Protein, *Arch Int Med* **44** 486 (Oct) 1929. (d) Gros, W. Zur Frage gesetzmässiger Veränderungen des Bluteiweissbildes beim multiplen Myelom, *Deutsches Arch f klin Med* **177** 461, 1935. (e) Weinberg, F., and Schwarz, E. Die Klinik und pathologische Anatomie des multiplen Myeloms, *Virchows Arch f path Anat (supp)* **227** 88, 1920. (f) Peilzweig, W. A., Delrue, G., and Geschickter, C. Hyperproteinemia Associated with Multiple Myelomas. Report of an Unusual Case, *J A M A* **90** 755 (March 10) 1928. (g) Patek, A. J., and Castle, W. B. Plasma Cell Leukemia, *Am J M Sc* **191** 788, 1936. (h) Kleine, H. O. Kristalloide Riesenzellen in Harnkanälchen bei plasmazellulärem Myelom, *Beitr z path Anat u z allg Path* **79** 678, 1928.

28 Lewis, D. Multiple Myeloma, *Internat Clin* **1** 157, 1927.

29 Schumacher, I. C., Williams, O. O., and Coltrin, G. S. Plasma Cell Myeloma and Hyperproteinemia, *California & West Med* **47** 174, 1937.

30 Jeghers, H., and Selesnick, S. Hyperproteinemia. Its Significance, *Internat Clin* **3** 249, 1937.

content of the blood never exceeded 9 per cent, whereas in the cases of multiple myeloma it varied between 9.4 and 12.2 per cent. Although it is true, as Bing³¹ wrote, that "in most cases hyperproteinemia will be a sign of myelomatosis," it must be remembered that the symptom may occur with a few other diseases, notably with kala-azar and lymphogranuloma venereum, and occasionally leprosy and cirrhosis of the liver.

In the present case the highest serum protein value was 14.9 per cent, of which 11.8 per cent was globulin and only 3.1 per cent albumin. Evidently the hyperproteinemia was purely hyperglobulinemia, just as it was in other cases reported.

In contrast to other writers, Chester³² reported a low serum protein level in 2 cases of multiple myeloma. He expressed the belief that the total protein of the blood plasma diminished in the late stages of the disease and that hypoproteinemia would ensue if the patients were observed long enough. Feller and Fowler²¹ were unable to confirm this, and in my case, as well as in Sweigert's,^{27b} the highest amounts were found shortly before death.

Freund and Magnus-Levy³³ stated that excretion of Bence Jones protein in the urine is accompanied with a low or normal total amount of protein in the blood plasma. Conversely, as pointed out by Cantarow,³⁴ Bence Jones protein has been found only rarely in the presence of hyperproteinemia. Nielsen,³⁵ for example, reported 4 cases, 2 of hyperproteinemia without Bence Jones bodies in the urine and 2 of hypoproteinemia with abundant Bence Jones protein. Several other authors,³⁶ however, have reported the coexistence of Bence Jones proteinuria and hyperproteinemia, and one of Gross and Vaughan's³⁷ patients had normal blood protein but no Bence Jones protein in the

31 Bing, J. Some Cases of Hyperproteinemia, *Acta med Scandinav* **88** 478, 1936.

32 Chester, W. Multiples Myelom und Hypoproteinämie, *Ztschr f klin Med* **124** 466, 1933.

33 Freund, R., and Magnus-Levy, A. Multiple Myeloma. V. Ueber Besonderheiten der Blutzusammensetzung, *Ztschr f klin Med* **121** 1, 1932.

34 Cantarow, A. Bence-Jones Proteinemia in Multiple Myeloma, *Am J M Sc* **189** 425, 1935.

35 Nielsen, H. E. Four Cases of Myelomatosis, *Hospitaltid* **81** 549, 1938.

36 (a) Stewart, A., and Weber, F. P. Myelomatosis, *Quart J Med* **7**. 211, 1938. (b) Decherd, G. M., and Holland, L. Multiple Myeloma with Hyperglobulinemia, *J Trop Med* **41** 129, 1938. (c) Shirer, J. W., Duncan, W., and Haden, R. L. Hyperproteinemia Due to Bence-Jones Protein in Myelomatosis, *Arch Int Med* **50** 829 (Dec.) 1932. (d) Feller and Fowler²¹.

37 Gross, R. E., and Vaughan, W. W. Plasma Cell Myeloma. Report of Two Cases with Unusual Survivals of Six and Ten Years, *Am J Roentgenol* **39** 344 (March) 1938.

urine My case was similar in this respect to the first 2 of Nielsen's cases The blood protein level was increased, and Bence Jones protein was absent

CALCIUM AND PHOSPHORUS

The serum calcium level has been reported high in a number of cases of multiple myeloma, with serum phosphorus normal or slightly elevated This relation, although present in only some of the cases, serves to differentiate multiple myeloma from hyperparathyroidism According to Gutman and Gutman,³⁸ the hypercalcemia is not brought about by a mere increase of the calcium bound to an excess of globulin but is the result of destruction of bone by the neoplasm Serum calcium in my case was normal (9.9 and 10 mg per hundred cubic centimeters on two determinations), despite an excess of serum globulin, but phosphorus was increased (4.2 and 7.5 mg per hundred cubic centimeters) In this my case was similar to several other reported cases³⁹ Low serum phosphorus and high calcium, however, a combination that is typical of hyperparathyroidism, may rarely be found with multiple myeloma⁴⁰

EXTRAOSSEOUS MYELOMA

The most striking feature of the case reported here was the presence of testicular tumors without other extraosseous involvement

Geschickter and Copeland⁴ in their review of all cases reported before 1928 did not mention metastases in the testicles⁴¹, neither did Magnus-Levy¹⁷ or Wallgren,³ both of whom cited numerous authors in their articles In an extensive survey of the literature on multiple myeloma I have seen only one mention of a testicular tumor This was in a case referred to by Porchownik⁴² as having been observed by Werzberg in Russia Large round nodules were found in the testis at necropsy Other details about the case were not given, so that doubt exists as to the diagnosis of myeloma In Ghon and Roman's⁴³ case

38 Gutman, A. B., and Gutman, E. B. Calcium-Protein Relation in Hyperproteinemia. Total and Diffusible Serum Calcium in Lymphogranuloma Inguinale and Myeloma, *Proc Soc Exper Biol & Med* **35** 511, 1936

39 Howard, C. X-Ray Aspects of Endotheliosis, read before the Eleventh Annual Fortnight of the New York Academy of Medicine, Oct 27, 1938. Multiple Myeloma, Cabot Case 21052, *New England J Med* **212** 204, 1935. Forbus and others¹⁹. Cantarow³⁴

40 Multiple Plasma Cell Myeloma, Cabot Case 23171, *New England J Med* **216** 757, 1937

41 The case to which they referred briefly in the revised edition of their book¹⁸ is the one I am reporting in this article

42 Porchownik, J. B. Ein Fall von multiplem Myelom (Plasmocytom), *Virchows Arch f path Anat* **280** 534, 1931

43 Ghon, A., and Roman, B. Ueber pseudoleukamische und leukamische Plasma-Zellen-Hyperplasie, *Folia haemat* **15** 72, 1913

scattered plasma cells were found in the right testis, but no gross tumor was seen ⁴⁴

Evidently, then, involvement of the testicles is rare with multiple myeloma, and I believe that the case reported here, in which the testicular lesion was the only extraosseous gross manifestation of the neoplasm, is unique in this respect, unless in the case cited by Polchownik the involvement was similar

Opinions differ about the origin of extraosseous myeloma. There are four possibilities: (1) direct extension of an intraosseous tumor to adjacent tissues, (2) metastasis, (3) independent (autochthonous) development, parallel with but not secondary to medullary growth, ⁴⁵ (4) primary extramedullary tumor with or without secondary invasion of the bone marrow ⁴⁶

Direct extension is not rare. Metastasis also is generally accepted as occurring not infrequently, although Lubarsch ^{45a} and Hallermann ⁴⁶ maintained that the apparent metastases are in reality independent parallel developments, and Winkler ⁴⁷ and Horsch ⁴⁸ expressed the belief that even the multiple intraosseous tumors were not extensions or metastases but independently originating foci. It is interesting to record here that Borrmann ⁴⁹ in 1900, when no case of growth outside the bones

44 M. B. Schmidt (*Allgemeine Pathologie und pathologische Anatomie der Knochen*, *Ergebn d allg Path u path Anat* **7** 220, 1900-1901) has been cited by several writers as reporting a case of multiple myeloma with testicular involvement. I have failed to find mention of myelomatous tumor of the testis in his article. It appears that the error was brought about by the fact that Isaac (*Die multiplen Myelome*, *Ergebn d Chir u Orthop* **14** 325, 1921) in his review referred to three articles by Schmidt, without specifying in which the testicular lesion was noted. The second of the three references was to Schmidt's monograph (*Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen*, Jena, Gustav Fischer, 1903) in which he reported the case of a boy of 16 with a testicular tumor, but the diagnosis was lymphosarcoma of the thymus with lymphatic infiltration of the testicles. Nowhere did I find a statement that the condition was multiple myeloma. Apparently authors writing after Isaac had copied the first of his three references without troubling to consult the original for verification.

45 (a) Lubarsch, O. *Zur Myelomfrage*, *Virchows Arch f path Anat* **184** 213, 1906. (b) Pines, L., and Pirogowa, L. *Ueber die multiplen Myelome und das Nervensystem*, *Arch f Psychiat* **84** 332, 1928. (c) Zadek, I., and Lichtenstein, H. *Zur Klinik und Zytologie der multiplen Myelome*, *Folia haemat* **45** 60, 1931. (d) Wallgren ³

46 Hallermann, W. *Zur Kenntnis des primären multiplen Myeloms*, *Deutsches Arch f klin Med* **165** 57, 1929.

47 Winkler, K. *Das Myelom in anatomischer und klinischer Beziehung*, *Virchows Arch f path Anat* **161** 252, 1900.

48 Horsch, K. *Multiple Myelome und metastatische Knochenmarkstumoren*, *Beitr z klin Chir* **161** 195, 1935.

49 Borrmann, R. *Myelom*, *Ergebn d allg Path u path Anat* **7** 852, 1900-1901.

had been reported, predicted that some day metastases to internal organs would be found. He expressed the thought that patients with multiple myeloma usually did not live long enough for metastases to develop and that myeloma cells did not find suitable soil in organs other than the bone marrow.

It is tempting to look on the case presented here as one of primary tumor of the testicle with secondary invasion of the bone marrow, because the testicular tumor had become clinically recognizable when definite roentgen evidence of osseous involvement was still lacking. Jackson, Parker and Bethea⁵⁰ wrote regarding their remarkable case, in which a plasmacytoma of the tonsil preceded medullary involvement by eight years.

There would seem to be no doubt but that the plasma-cell tumor arose in the tonsil, spread through the lymphatic system, and finally reached the marrow.

In Kreibich's⁵⁰ case the first indication of the disease was a wartlike growth on the skin, not until eight weeks later was involvement of the bones demonstrated. Magnus-Levy¹⁷ did not accept this case as one of primary extraosseous involvement, stating the belief—correct, I think—that the growth in the marrow could have existed weeks before it was recognized and that it was probably older than the tumor of the skin. For similar reasons he rejected Kijukoff's⁵¹ and von Weidt's⁵² cases. He has insisted that the relative size of the tumors does not determine their chronologic age, because some of them grow more rapidly than others. He stated also, however, what was first suggested by Boir-mann,⁴⁹ that myelomatous tissue grows poorly outside the bone marrow and that the neoplastic cells find nourishment and favorable growth only in the tissues of their ultimate origin (*ursprünglichen Mutterboden*) or in connection with it, and outside it only in the similar tissue of the lymph nodes.

In my case the tumors in the testes grew more rapidly than would be expected if Magnus-Levy's statement regarding the relative speed of growth of intraosseous and extraosseous lesions were always true, but the fact that the first tumor to be recognized in the testicle (by the patient himself) was relatively large when involvement of the bones could not yet be demonstrated by roentgen examination cannot be accepted, it seems to me, as proof of its primacy. At necropsy the intraosseous growth was found to be diffuse and not in the form of grossly recognizable nodules. Such a diffuse growth could have begun before the

50 Kreibich, C. Plasmomyelom der Haut, *Folia haemat* **18** 94, 1914.

51 Kijukoff, A. Le plasmocytome histogene, *Folia haemat* (pt 1) **12** 372, 1911.

52 von Weidt, F. Zum Kenntnis des Plasmocytoms, *Frankfurt Ztschr f Path* **6** 180, 1910-1911.

testicular tumor, or it could have developed simultaneously with it, and, to satisfy Magnus-Levy's dictum, it could have grown and probably did grow more rapidly than the tumor in the testis without being recognizable roentgenologically for a relatively long time because of its diffuseness.

It is of more than academic interest to determine whether a myeloma is single and primary, because treatment of such a circumscribed growth may prevent progression or recurrence of the disease. Thus, Mathias' ⁵³ patient was free from symptoms eighteen months after surgical removal of a localized myeloma of the skull. Bailey ⁵⁴ irradiated a single myeloma of the humerus, after which the patient, observed six years later, was apparently cured. In Shaw's case of a similar tumor ⁵⁵ simple curettement was followed by healing and no signs of recurrence a year later. Rogers' ⁵⁶ patient, with a solitary myeloma of the right femur, was well four years after amputation of the leg.

NATURE OF MYELOMA CELLS

The nature of the cells involved in the formation of multiple myeloma has been the subject of much study, discussion, speculation and controversy. Wallgren ⁵⁷ has pointed out that they have been called lymphocytes, lymphoblasts, ⁵⁸ myelocytes, myeloblasts, plasma cells and erythroblasts ⁵⁹. Seemann ⁶⁰ expressed the belief that in myeloma there may be a hyperplasia of lymphoidocytic (myeloblastic) tissue at first, which later, for as yet unknown reasons, undergoes plasmacytic transformation. Williams ⁶¹ advanced the suggestion that "certain biological properties of the osteoblast point to it as a possible cell of origin" of the myeloma cells. Gunn and Mahle ⁶² reported a case in which they believed

53 Mathias, E. Zur Myelomfrage, Beitr. z. klin. Chir. **161** 79, 1935.

54 Bailey, C. O. Plasma Cell Myeloma of the Humerus Treated by Roentgen Radiation, Am. J. Roentgenol. **36** 980, 1936.

55 Shaw, A. F. B. A Case of Plasma-Cell Myeloma, J. Path. & Bact. **26** 125, 1923.

56 Rogers, H. Case of Solitary Plasma-Celled Myeloma, Brit. J. Surg. **17** 518, 1930.

57 Wallgren, A. Ueber die Natur der Myelomzellen, Vuchows Arch. f. path. Anat. **232** 381, 1921.

58 Klemperer, P. Ueber das lymphoblastische und das plasmacellulare Myelom, Beitr. z. path. Anat. u. z. allg. Path. **67** 492, 1920.

59 Harbitz, F. Erythroblastosis and Erythroblastoma, Norsk mag. f. lægevidensk. **84** 211, 1923. Grogler, F. Zur Kenntnis des Myeloms, Frankfurt Ztschr. f. Path. **43** 96, 1932.

60 Seemann, G. Ein Fall von plasma-zellularem "Myelom," Centralbl. f. allg. Path. u. path. Anat. **48** 212, 1930.

61 Williams, H. W. Multiple Myeloma of Bone, Am. J. Cancer **16** 540, 1932.

62 Gunn, F. D., and Mahle, A. E. Megakaryoblastic Myeloma with Crystalline Protein in the Renal Tubules, Tr. Chicago Path. Soc. **15** 23, 1937.

the changes to be megakaryoblastic. Of 643 cases reviewed by Atkinson,⁶³ the cytologic changes in 332 were not classified, in 207 they were plasmocytic, in 27 myeloblastic, in 24 myelocytic, in 16 lymphocytic, in 5 erythroblastic, in 28 mixed and in 4 of doubtful type. Wallgren³ expressed the opinion, which seems plausible, that a lymphocytic type does not exist, that newer methods of staining have done away with it, and that all myelomas are made up of cells of the same fundamental type, which may, however, show certain varying stages of development, differentiation or degeneration. Ewing⁶⁴ seems to have been in agreement with that when he wrote that multiple myeloma is a "specific malignant tumor of the bone marrow arising probably from a single cell-type." Hirschfeld⁶⁵ also expressed doubt about the existence of a lymphocytic type, suggesting that myelocytes may have been mistaken for lymphocytes. Nevertheless, Rosenblum and Kirshbaum⁶⁶ in 1936 and Stewart and Weber^{66a} in 1938 reported cases of what they called lymphocytic myeloma and Dameshek⁶⁷ included multiple myeloma in the group of tumors arising from lymphoid tissue. This is contrary to the classification by the Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists,⁶⁸ in which myelomas are grouped with the myeloid tumors, and the term multiple myeloma is used as a synonym of multiple aleukemic myelocytoma.

In a large proportion of the cases the component cells, with their deeply basophilic cytoplasm and often eccentrically placed nuclei, resemble plasma cells more closely than any other known form of cell, hence the designations plasmacytoma, plasmoma, multiple myeloma of the plasma cell type and plasmacytic leukemia⁶⁹ have been applied. Often, however, the cells lack certain characteristics of typical plasma cells. The nucleus frequently does not have the coarse radial arrangement of the chromatin, the perinuclear *Hof* is often absent, and the characteristic staining reaction of plasma cells may be lacking. In view of their uncertain identity, Wallgren³ suggested that they be spoken of merely

63 Atkinson, F. R. B. Multiple Myelomata, *M. Press* 195 312 and 327, 1937

64 Ewing, J. Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928

65 Hirschfeld, H. Ueber die multiplen Myelome, *Folia haemat.* 9 1, 1910

66 Rosenblum, A. H., and Kirshbaum, J. D. Multiple Myelomas with Tumor-Like Amyloidosis. Clinical and Pathologic Study, *J. A. M. A.* 106 988 (March 21) 1936

67 Dameshek, W. Progress in Hematology in 1936, *New England J. Med.* 218 15, 1938

68 Callender, G. R. Tumors and Tumor-like Conditions of the Lymphocyte, the Myelocyte, the Erythrocyte and the Reticulum Cell, *Am. J. Path.* 10 443, 1934

69 (a) Piney, A. Plasma Cell Leukemia, *Folia haemat.* 30 173, 1924 (b) Osgood, E. E., and Hunter, W. C. Plasma Cell Leukemia, *ibid.* 52 369, 1934 (c) Gluzinski, A., and Reichenstein, M. Myeloma und Leucaemia lymphatica plasmacellularis, *Wien klin. Wchnschr.* 19 336, 1906

as myeloma cells Zadek and Lichtenstein,⁷⁰ Hallay and Odor⁷⁰ and others⁷¹ expressed the same opinion According to Zadek and Lichtenstein, the cells that form myeloma are not normal bone marrow cells—that is, they are neither typical myeloblasts, nor lymphoblasts nor characteristic plasma cells The cells are abnormally differentiated (*entdifferentierte*) cells derived from the bone marrow, which in accordance with Wallgren's suggestion, are to be designated myeloma cells

Transitional types between myeloblasts and plasma cells were seen in the case reported here, as in the cases of Cappell⁷² and others⁷³ Christian^{73a} wrote

It seems possible to arrange the cells of these tumors in series so that between the cells of succeeding cases the differences are slight, though the differences between the cells at the extremes are fairly great

That "myeloma cells" are related to myeloid cells is indicated by the fact that Forman and Warren⁷⁴ and Beck and McCleary⁷⁵ reported cases in which the peroxidase reaction was positive In others, however, as, for example, Moise's⁷⁶ 3 cases and Burnett and Johnson's⁷⁷ case, the reaction was negative Since the test is not reliable for very young cells, a negative reaction is without differential diagnostic value

Zadek⁷⁸ and others⁷⁹ offered the opinion, based on studies of marrow obtained by sternal puncture, that plasma cells are derived, even normally, from the reticuloendothelial stroma of the bone marrow, and that myeloma cells have the same origin

70 Hallay, I, and Odor, B Ueber einen Fall von multiplem Myelom, *Ztschr f klin Med* **120** 32, 1932

71 (a) Markoff, N Die Beurteilung des Knochenmarks durch Sternalpunktion, *Deutsches Arch f klin Med* **179** 113, 1936 (b) Curtze, W Untersuchungen uber multiple Myelome, *Folia haemat* **60** 1, 1938 (c) Heilmann, P Beitrag zur Myelomfrage, *Centralbl f allg Path u path Anat* **58** 405, 1933

72 Cappell, D F Two Cases of Myelomatosis (1) Diffuse Plasma-Celled, (2) with Tumour-like Nodules and Visceral Lesions, *J Path & Bact* **32** 293, 1929

73 (a) Christian, H A Multiple Myeloma A Histological Comparison of Six Cases, *J Exper Med* **9** 325, 1907 (b) Krjukoff⁵¹

74 Forman, J, and Warren, J H The Identification of the Cells in Myelomas by Means of the Indol-Phenol Blue Synthesis, *J Cancer Research* **2** 79, 1917

75 Beck, H G, and McCleary, S Multiple Myeloma with Bone Marrow Plasma Cells in the Blood, *J A M A* **72** 480 (Feb 15) 1919

76 Morse, P F The Peroxidase Reaction in Three Cases of Multiple Myeloma of the Bones with Remarks Concerning the Nosological Position of the Tumors, *J Cancer Research* **5** 345, 1920

77 Burnett, C T, and Johnson, W C Multiple Myeloma, *Colorado Med* **27** 178, 1930

78 Zadek, I Die hamatologische Diagnose des multiplen Myeloms, *Wien klin Wchnschr* **51** 632, 1938

79 Rohr, K Blut- und Knochenmarksmorphologie der Agranulocytosen, *Folia haemat* **55** 305, 1936 Curtze^{71b}

Support for the contention that only one type of cell is involved in all cases of multiple myeloma is found in the fact, which has been pointed out by others,⁸⁰ that in recent years the number of reports of plasmacytoma, compared with other types, has increased. Thus, Wallgren⁵⁷ found that of the 25 cases reported between 1900 and 1904, in only 3 was a diagnosis of plasmacytoma made, whereas in half of the 30 cases between 1905 and 1909 and 15 of the 25 between 1910 and 1914 that designation was given. Fleischhacker and Klima⁸¹ found that all but 1 of their 10 cases were instances of plasmacytoma, and the diagnosis in the exceptional case was not verified by necropsy.

The case reported here illustrates the difficulties that may be met. The testicular tumors and the bone marrow contained many so-called atypical plasma cells, and other cells, found also in the kidneys and spleen, appeared to be myelocytes and myeloblasts. However, I am convinced that all of them were variations of the same basic type. This is in accord with the views of Smith and Silberberg,⁸² who wrote regarding their case that the "multiple myeloma of the hemoblastic type consisted of a large variety of blood cells in various stages of differentiation" and stated:

It is only logical to assume that all the different cell types may have a common source. This progenitor cell, proliferating under tumor conditions, retains all its hematopoietic potentialities so that differentiation may take place in all directions and a most varied cytologic structure result.

Patek and Castle²⁷⁸ stressed "the desirability of regarding this plasma cell tumor (plasmacytoma) as a pathologic entity whose different forms are not distinct diseases, but are simply gradations in extent and activity of the same disease process." From a histologic standpoint, therefore, multiple myeloma may be regarded as an entity. This does not mean that attempts to recognize subgroups or variations (erythroblastic, myeloblastic and plasmacytic) should be abandoned. I agree with Pentman⁸⁰ that there are differences in type but not necessarily in origin.

RELATION OF MYELOMA TO LEUKEMIA

The diffuse nature of the medullary growth in this and other reported cases⁸³ strengthens the belief that multiple myeloma is related to the

80 Pentman, I. Beitrag zu den multiplen Myelomen, *Virchows Arch f path Anat* **258** 161, 1925. Mathias⁵³ Seemann⁶⁰

81 Fleischhacker, H., and Klima, R. Beitrag zur Kenntnis des multiplen Myeloms, der plasmacellularen Leukämie und des plasmacellularen Granuloms, *Folia haemat* **56** 5, 1936.

82 Smith, R. P., and Silberberg, M. Multiple Myeloma of Hemocytoblastic Type, *Arch Path* **21** 578 (May) 1936.

83 Jochmann, G., and Schumm, O. Zur Kenntnis des Myeloms und der sogenannten Kahler'schen Krankheit, *Ztschr f klin Med* **46** 445, 1902. Abrikosoff, A., and Wulff, F. Ueber Erweisskristallbildung in einem Fall von Myelom, *Verhandl d deutsch path Gesellsch* **22** 270, 1927.

leukemias The testicular tumors in the present case were not circumscribed but resembled the extramedullary nodular infiltrations found in the internal organs in some cases of leukemia (fig 2) Foord and Randall^{7b} found a leukemia-like growth of plasma cells in the spleen, lymph nodes, liver and adrenal glands Seemann⁶⁰ has pointed out the similarity between myeloma and chloroma Battaglia,⁸⁴ Piney and Riach⁸⁵ and Osgood and Hunter^{69b} called attention to the morphologic gradations in the development of myelomatous tissue, from solitary or scattered circumscribed nodules to diffuse hyperplasia, the latter closely resembling leukemia According to Hamman,⁸⁶ multiple myeloma "belongs to that remarkable group of diseases that stand midway between the leukemias and the malignant tumors"

In several reported cases⁸⁷ the "myeloma cells" have been observed in the circulating blood, in 1 case making up as much as 70 per cent of the leukocytes^{69c} In my case the greatest concentration found at any time was 10 per cent (fig 4) In addition, there were some unclassified cells, some or all of which probably belonged to the same category Osgood and Hunter^{69b} expressed the belief that their patient, with 54 per cent "plasma cells" in the blood, had plasmacytic leukemia rather than multiple myeloma I doubt that such a differentiation was warranted It is more likely that the difference was merely one of diffusion or of circumscription of the same fundamental pathologic process

Vance⁸⁸ in 1916 wrote that in "no case have myelocytes been found in the circulating blood" That is no longer true Several writers have since then reported the presence not only of myelocytes but of myeloblasts in the peripheral blood In the case presented here they were present almost constantly (fig 4), making up from 2 to 19 per cent of the leukocytes It was because of this that the differentiation from myeloid leukemia was not established until histologic study of the testicular tumor and necropsy material had been made Such a differ-

84 Battaglia, F Beitrag zur Kenntnis der Systemerkrankungen des Knochenmarks (Myelom und aleukämische Myelose), *Virchows Arch f path Anat* **267** 106, 1928

85 Piney, A, and Riach, J S Multiple Myeloma Aleukemic and Leukemic, *Folia haemat* **46** 37, 1931

86 Hamman, L, in discussion on Scott, J W Multiple Myeloma, *South M J* **17** 478, 1924

87 Muller, G L, and McNaughton, E Multiple Myeloma (Plasmacytomata) with Blood Picture of Plasma Cell Leukemia Report of Two Cases, *Folia haemat* **46** 17, 1931 Jores, A, and Bruns, W Ein Fall von "malignem Plasmom" mit einem Beitrag zur sogenannten "Plasmazellenleukämie," *ibid* **55** 227, 1936 Ghon and Roman⁴³ Footnote 69 b and c Fleischhacker and Klima⁸¹ Piney and Riach⁸⁵

88 Vance, B M A Case of Multiple Myelomata, with a Discussion of Its Nature and Origin, *Am J M Sc* **152** 693, 1916

entiation may be difficult and, perhaps, not always warranted. Strong supporting evidence of the similarity and close relation of these diseases is supplied by Furth's⁸⁹ experiments with mice, in which, after injection of a transmissible strain of myeloid leukemia, leukemia developed in some animals and myeloma in others. Among the differences between the two conditions, Battaglia⁸⁴ mentioned the greater tendency of leukemia to infiltrate extraosseous tissues and of myeloma to destroy bone and to form nodules. Despite these differences the evidence is against Deelman's⁹⁰ terse dictum: "Myeloma is a tumor, leukemia is not a tumor."

The following suggested classification of myelomas emphasizes the transition and relation between various types, bordering at one extreme on the definite neoplastic tumors and at the other on leukemia.

1 Solitary benign tumor in or out of the bone marrow, which may be amenable to surgical removal or irradiation with hope of cure.

2 Single or multiple malignant tumor of the bones, with or without extraosseous growth.

3 Diffuse myelomatosis of the bone marrow, with or without infiltration of other organs.

4 "Plasmacytic" leukemia.

This schema is in agreement with the idea Waugh⁹¹ expressed about the "interrelation of various systemic hematopoietic processes," according to which they "form a quite definite series which blends from one into the other." Schmidt⁹² wrote as long ago as 1900 that a close relation existed between myeloma and pseudoleukemia on the one hand and sarcoma on the other, and that with these as well as with lymphoma and lymphosarcoma it is not easy to draw the line between hyperplasia and true tumor.

Certain experimental studies lend strong support to the conception of unitarian origin of the various forms of myeloma and of its intermediate position between frank tumor and diffuse hyperplasia. Fischer-Wasels⁹³ produced a variety of lesions, including lymphosarcoma and myeloid leukemia, in mice subjected to mild but prolonged poisoning with indole. More recently Furth,⁹⁴ experimenting with the transmis-

89 Furth, J. Transmission of Myeloid Leukemia in Mice. Its Relation to Myeloma, *J. Exper. Med.* **61** 423, 1935.

90 Deelman, H. T. Myeloma in Relation to Leukemia, *Nederl. tijdschr. v. geneesk.* **80** 118, 1936.

91 Waugh, T. R. The Interrelation of Various Systemic Hematopoietic Processes, *Am. J. M. Sc.* **193** 337, 1937.

92 Schmidt, cited in footnote 44.

93 Fischer-Wasels, B. Experimentelle Grundlagen und Folgerungen der Regenerationstheorie der Geschwulstbildung, *Klin. Wchnschr.* **11** 1977, 1932.

94 Furth, J. Transmission of Myeloid Leukemia in Mice, *Proc. Soc. Exper. Biol. & Med.* **31** 923, 1934.

sion of myeloid leukemia in mice, found that he could produce localized tumors or extensive, more or less diffuse infiltration of several organs and the presence of leukemic cells in the circulating blood, depending on whether the injections were made subcutaneously or intravenously. These results were confirmed by Kaalund-Jørgensen.⁹⁵ Furth, Seibold and Rathbone⁹⁶ obtained similar results with lymphomatosis of mice. More important still in this connection are the previously cited additional experiments of Furth,⁸⁹ in which intravenous injection of a transmissible strain of myeloid leukemia in mice resulted in the development of diffuse myelosis in some of the animals and of multiple myeloma in others.

SUMMARY AND CONCLUSIONS

A case of multiple myeloma is reported in which there were certain noteworthy features, including tumors in the testes, absence of pain, absence of definite roentgen evidence of the disease in the bones, presence of myeloma cells in the circulating blood and hyperproteinemia without Bence Jones proteinuria. As a result of a study of this case and a review of the literature, certain conclusions may be drawn:

- 1 Multiple myeloma is a neoplastic disease occupying a position midway between frank tumors and diffuse (leukemic) hyperplasia. The growths are composed of cells of myeloid origin, which usually resemble plasma cells and which may differentiate in varying directions to form apparently distinct types of the disease.

- 2 The usual site of origin is the bone marrow but extramedullary origin may occur.

- 3 The outstanding symptoms are pain and weakness, but pain may not develop until injury to a diseased bone occurs, it is usually absent in extraosseous lesions and may not be present when the process in the bone marrow is diffuse. Multiple myeloma should be thought of as a possible cause of unexplained pain in various parts of the body, especially backache.

- 4 Renal disease is a common complication of multiple myeloma. In some cases it appears to be a form of hydronephrosis secondary to tubular obstruction by casts of Bence Jones protein, in others the mechanism of its production is not known.

- 5 Treatment in the majority of cases is wholly symptomatic, exposure to roentgen rays may be effective in relieving pain. The prognosis is hopeless, except in the occasional cases of solitary tumor, in which surgical removal or roentgen therapy may result in cure.

⁹⁵ Kaalund-Jørgensen, O. Eine überimpfbare Myelomatose der Maus, *Ztschr f Krebsforsch* **42** 393, 1935.

⁹⁶ Furth, J., Seibold, H. R., and Rathbone, R. R. Experimental Studies on Lymphomatosis of Mice, *Am J Cancer* **19** 521, 1933.

6 Examination by means of roentgen rays is one of the most important diagnostic procedures, although the radiologist may be unable to differentiate between myeloma and metastatic carcinoma⁹⁷ Other methods of examination may be of equal or even greater value They may confirm a suspicion of myeloma, or they may suggest the diagnosis when it had not been thought of before They include

(a) Biopsy of an involved portion of bone It establishes the diagnosis with reasonable certainty if it shows the presence of typical myeloma cells

(b) Sternal puncture It may reveal the characteristic cells, even when the sternum is not grossly affected

(c) Hyperproteinemia A serum protein level of more than 10 per cent is unusual with other diseases

(d) Hypercalcemia, with a normal or high serum phosphorus level This combination distinguishes multiple myeloma from hyperparathyroidism

(e) Bence Jones proteinuria Although absent in many cases and present occasionally with other diseases, it is strong presumptive evidence of multiple myeloma

(f) The presence of myeloma cells ("atypical plasma cells") in the circulating blood They are usually absent, but may be present in large numbers and may then be the first definite sign pointing to the correct diagnosis

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⁹⁷ Holmes, G W, in discussion on Multiple Myeloma, Cabot Case 23122, New England J Med **216** 521, 1937

LIPOCAIC AND FATTY INFILTRATION OF THE LIVER IN PANCREATIC DIABETES

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In 1924 Fisher ¹ and Allan, Bowie, Macleod and Robinson ² reported that completely depancreatized dogs adequately treated with insulin usually failed to survive more than two to three months. At autopsy the most prominent change observed was an extensive fatty infiltration and degeneration in the liver. In general these findings have been widely confirmed. Occasional animals have been observed in which the fatty changes developed and death occurred in five to six weeks, while others have survived for six months to a year and still others have failed to show any evidence of disease of the liver and have survived for long periods with no supplementary treatment other than the insulin therapy. The latter constitute a small minority and will be discussed later. The addition of raw pancreas to the diet of the depancreatized dog was found by Allan, Bowie, Macleod and Robinson to prevent or relieve the fatty changes in the liver and to permit the animal to survive indefinitely when treated also with insulin. In 1936 Dragstedt, Van Prohaska and Harms ³ reported that the beneficial effect of feeding pancreas in this connection could not be accounted

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1 Fisher, N F. Am J Physiol **67** 634, 1924

2 Allan, F N, Bowie, J J, Macleod, J J R, and Robinson, W L. Brit J Exper Path **5** 75, 1924

3 Dragstedt, L R, Van Prohaska, J, and Harms, H P. Am J Physiol **117** 175, 1936

for on the basis of its content of pancreatic enzymes or of choline but was due to a specific substance, believed to be a new hormone. The name lipocaic was suggested for this substance. It is the purpose of the present report to present further evidence which indicates that lipocaic is an internal secretion of the pancreas.

FATTY CHANGES IN THE LIVER IN DIABETES MELLITUS AND IN PANCREATIC DIABETES

The occurrence of fatty changes in the liver in diabetes mellitus has apparently long been known and was described from time to time in the older literature. More recently (1931) Meyer⁴ reported that hepatic dysfunction was frequent in diabetes mellitus and that in 28 per cent of the series of cases studied by him there was either laboratory or clinical and laboratory evidence of impairment of the liver. In contrast to other observers, he concluded that the older the patient and the longer the diabetes mellitus remained uncontrolled, the more frequently hepatic dysfunction became demonstrable. White⁵ (1932) remarked that fatty infiltration of the liver in diabetic children was common and presented roentgen evidence of decrease in its size after administration of insulin and dietetic management. Hanssen⁶ (1936) found marked enlargement of the liver in 12 of a series of 44 diabetic patients under 20 years of age. Here also the enlargement receded under better control of the diabetes by the use of protamine zinc insulin and a diet relatively low in carbohydrate.

Von Mehring and Minkowski⁷ (1890) called attention to the accumulation of fat in the liver in depancreatized dogs that died of diabetes, and a vivid picture of this condition was given by Naunyn⁸ (1906), who likened the microscopic appearance to that of the liver in the most severe type of phosphorus poisoning. These observations were confirmed by many workers in the period before the isolation of insulin, and we have seen the manifestation many times.

4 Meyer, E. L. Function of the Liver in Diabetes Mellitus. *Arch. Int. Med.* **47**: 182 (Feb.) 1931.

5 White, P. Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 169.

6 Hanssen, P. Enlargement of the Liver in Diabetes Mellitus, *J. A. M. A.* **106**: 914 (March 14) 1936.

7 von Mehring, J., and Minkowski, O. *Arch. f. exper. Path. u. Pharmacol.* **26**: 371, 1890.

8 Naunyn, B. *Der Diabetes mellitus*, ed. 2, Vienna, Alfred Holder, 1906, p. 118.

FATTY INFILTRATION OF THE LIVER IN DEPANCREATIZED DOGS
DUE TO POOR CONTROL OF THE DIABETES BY INSUFFICIENT
AMOUNTS OF INSULIN AND FATTY CHANGES IN THE
LIVER DUE TO LIPOCAIC DEFICIENCY

The recognition of the occurrence of fatty infiltration of the liver both in diabetes mellitus and in pancreatic diabetes due to inadequate administration of insulin raised the question as to the relation of this type of fatty liver to that due to lipocaic deficiency. The following experiments were done to give some information on this problem.

Complete pancreatectomy was performed on 2 dogs and a diet of bread, meat and milk provided, but no insulin given. At the time of operation the livers were observed to be normal in size and color, and microscopic examination of biopsy specimens showed the usual minimum amount of fat. One animal was killed after forty-eight hours and the other after seventy-two hours. A marked fatty infiltration in the liver (graded 4 plus) was found in each case. Pancreatectomy was then performed on 3 additional animals. In each case the liver was observed to be of normal color and size at operation, and sections stained for fat showed no fat or a few fine granules. The diet was again bread, meat and milk, and no insulin was administered. After twenty-four hours a biopsy was made of the liver of 1 animal and a definite fatty infiltration (graded 2 plus) was found. After the biopsy this animal was placed on protamine zinc insulin therapy and the diabetes well controlled. After nineteen days of such treatment a second biopsy was made, and at this time the liver was found to be normal. The diet and insulin treatment were then continued as before for sixty-six days. The animal then began to show evidence of lipocaic deficiency (decreased excretion of dextrose, increased sensitivity to insulin and decreased activity), and a third biopsy of the liver disclosed a return of fat in the liver, more marked than before (graded 3 plus). The course of events for the other 2 depancreatized dogs was similar. Both showed marked fatty infiltration of the liver (graded 4 plus) in twenty-four and in ninety-six hours when given no insulin. Good control of the diabetes with protamine zinc insulin produced a complete removal of fat from the liver in 1 animal in nine days and a marked reduction in the other in four weeks. In each case the insulin treatment was continued, but in spite of this a reaccumulation of fat occurred in the liver in forty-five and in ninety-three days in these 2 animals. Both showed the usual signs of lipocaic deficiency, and both responded to the oral administration of lipocaic by increased excretion of dextrose, increased insulin tolerance and removal of fat from the liver.

Numerous other observations have been made which confirm the findings in the experiments just described. These may be summarized

in the following general statement. An immediate and marked accumulation of fat occurs in the liver cells of dogs within the first two or three days after complete pancreatectomy. This is particularly striking in well nourished or fat animals and when no insulin or relatively small doses are given and a large excretion of dextrose occurs. Such animals often exhibit marked lipemia (total lipids reaching 2 to 3 per cent), and severe acidosis may occur. These abnormalities are probably to be attributed to poor control of the diabetes with insufficient amounts of insulin. They are promptly corrected when insulin is administered in a more adequate amount and manner. However, when this is done and treatment of the diabetes is carried out most carefully, there occurs a steadily lessening excretion of dextrose in spite of continually decreasing doses of insulin, until after six to eight weeks the animal may excrete only a gram or 2 per day and receive only 2 to 3 units of insulin. Larger amounts of insulin, even 5 units, may at this time provoke fatal hypoglycemic convulsions. Superficially it might appear as though the animal were recovering from the diabetes. However, progressive weakness and loss of appetite develop, the animal becomes emaciated, and death occurs. At autopsy the liver is found to be enlarged to three or four times its normal size and so infiltrated with fat that the normal structure is entirely obscured.

These findings suggest that two entirely distinct types of fatty liver develop in depancreatized dogs, one due to insulin deficiency and one due to lipocaic deficiency. As will be described in detail elsewhere, there appear to be definite histologic differences between the two types. In the type that appears early in depancreatized dogs treated inadequately with insulin, the normal lobular architecture is preserved and the fat is usually present in the liver cells in the form of fine granules or small droplets. In the type that appears later (in six to eight weeks as a rule), the structure of the liver is usually destroyed and large droplets of fat occupy the place of the liver cells. Evidence of impaired hepatic function, as revealed by the bromsulphalein test, is almost always present, whereas it is less common with fatty liver of insulin deficiency. The most significant difference between the two types, however, lies in the response to insulin. The animal with fatty liver due to poor control of the diabetes tolerates large doses of insulin well, and such treatment clears the liver of fat and reduces the hyperlipemia when this is present. The animal with fatty liver due to lipocaic deficiency displays commonly hypolipemia, and hypoglycemic convulsions develop with small doses of insulin. Furthermore, when such animals succumb to the insulin they still have the excessively fatty liver.

Evidence suggesting the occurrence of these two types of fatty infiltration of the liver in human diabetes mellitus has recently appeared

Grayzel and Radwin⁹ (1938) treated 3 young diabetic patients with hepatomegaly by means of lipocaic and secured a striking recession of the liver to its normal size. When the lipocaic was discontinued, the hepatomegaly returned, and it again receded when lipocaic therapy was resumed. The diabetes in these patients had been well controlled by diet and insulin therapy. Rosenberg¹⁰ (1938) reported a case in which marked hepatomegaly and impaired hepatic function in an adult with mild diabetes did not improve with better control of the diabetes by diet and insulin therapy. A biopsy specimen of the liver secured at operation revealed a marked fatty infiltration similar to that seen in the depancreatized dog. The administration of lipocaic brought about improvement in hepatic function, recession in the size of the liver and disappearance of the fat, as revealed by a second biopsy. Marble, White, Bogan and Smith¹¹ (1938) studied 60 cases of pronounced hepatomegaly among 1,077 diabetic children in Joslin's clinic and came to the conclusion that the manifestation resulted from fatty infiltration and was usually due to poor control of the diabetes. The oral administration of raw pancreas in 2 cases and of betaine hydrochloride in 12 produced little or no improvement, while better control of the diabetes by the use of protamine insulin did result in decrease in the hepatomegaly. It is noteworthy that the patients displayed no impairment of hepatic function and were not unusually sensitive to insulin, as is true of persons with fatty liver of lipocaic deficiency.

SURVIVAL OF COMPLETELY DEPANCREATIZED DOGS TREATED WITH
INSULIN WITHOUT THE ADDITION OF LIPOCAIC, CHOLINE
OR LECITHIN IN THE DIET

The conclusion independently arrived at by Fisher¹ (1924) and by Allan, Bowie, Macleod and Robinson² (1924) that the completely depancreatized dog would not survive more than a few months even though adequately treated with insulin was supported by the subsequent studies of Best and his associates¹². The data presented in a previous report

9 Grayzel, H. G., and Radwin, L. S. Hepatomegaly in Juvenile Diabetes Mellitus Treated with Pancreatic Extract, *Am J Dis Child* **56** 22 (July) 1938

10 Rosenberg, D. H. *Am J Digest Dis* **5** 607, 1938

11 Marble, A., White, P., Bogan, I. K., and Smith, R. M. Enlargement of the Liver in Diabetic Children, *Arch Int Med* **62** 740 (Nov) 1938. White, P., Marble, A., Bogan, I. K., and Smith, R. M. *ibid* **62** 751 (Nov) 1938

12 (a) Best, C. H., Channon, H. J., and Ridout, J. H. *J Physiol* **81** 409, 1934. (b) Best, C. H., Ferguson, G. C., and Hershey, J. M. *ibid* **79** 94, 1933. (c) Best, C. H., and Hershey, J. M. *ibid* **75** 49, 1932. (d) Best, C. H., Hershey, J. M., and Huntsman, M. E. *ibid* **75** 56, 1932. (e) Best, C. H., and Huntsman, M. E. *ibid* **75** 405, 1932. (f) Best, C. H., and Ridout, J. H. *ibid* **78** 415, 1933

from this laboratory¹³ were in harmony with this view. Eight depancreatized dogs treated with insulin and given a diet of meat, bread and milk and large amounts of pancreatic juice survived only twenty-four, forty-one, forty-five, fifty-six, sixty-five, sixty-eight, seventy-five and one hundred and forty-two days. All these animals were found to have extensive fatty infiltration of the liver at autopsy. We now have data on 154 depancreatized animals. In 92 per cent of the total number fatty changes in the liver were revealed by laparotomy and biopsy. In 4 of a later group insulin therapy and a diet of bread, whole milk and meat with the daily addition of cod liver oil and brewers' yeast but without lipocaic or choline supplements were continued. All died, in twenty-six, thirty-one, seventy-five and one hundred and fifty-five days, and at autopsy the liver in each case contained over 30 per cent fat by chemical analysis. In 13 of the 154 the liver remained normal on repeated examination. These animals were not given lipocaic or choline but were continued in the laboratory on various different diets. All eventually died, after intervals varying between two and seventeen months. It is thus evident that in a small proportion of insulin-treated depancreatized dogs (about 8 per cent in our series) the characteristic fatty changes in the liver do not develop. The reason for this is obscure. It is probably not due to the presence of accessory pancreatic tissue, since with a little experience it is not difficult for an observer to be sure that all pancreatic tissue is removed at operation, and the intramural portions of the pancreatic ducts have always been excised. In a recent paper Chaikoff and Kaplan¹⁴ (1937) reported that "When maintained with insulin and a high-calorie, high-protein, high-vitamin diet completely depancreatized dogs may survive for as long as 4 to 5 years," and that "This length of survival makes it unnecessary to assume that raw pancreas or extracts thereof or choline supplements (i e., in addition to that contained in the dietary constituents) are essential for the survival of the completely depancreatized dog receiving insulin." It is possible that the discrepancy between the conclusions of these workers and those we have made from our own data may be accounted for in part by the following quotation from their paper: "In order to avoid chronic undernutrition, animals that failed to regain a good appetite within a month or so after pancreatectomy were discarded." It has been our experience that insulin-treated depancreatized dogs suffering from lipocaic deficiency usually display, among other symptoms, a loss of appetite and decreased activity. This is regularly associated with a

13 Van Prohaska, J., Dragstedt, L. R., and Harms, H. P. *Am J Physiol* **117** 166, 1936.

14 Chaikoff, I. L., and Kaplan, A. *J Nutrition* **14** 459, 1937.

fatty liver and is promptly relieved by administration of lipocaic. For this reason among others it does not seem wise to us to discard part of the data in attempting to decide the usual course of the insulin-treated depancreatized dog.

As noted before, 92 per cent of 154 insulin-treated depancreatized dogs in our series showed fatty changes in the liver which could be attributed to lipocaic deficiency. Twelve of these, including the 8 animals reported on in a previous paper,¹³ were given no effective supplementary treatment, and all died within a few months. The great majority of the animals with fatty liver were given supplementary treatment with raw pancreas, various pancreas fractions, choline or betaine hydrochloride. In spite of this, a good many valuable data bearing on this question of survival have accumulated which because of limitations of space cannot be presented in detail. In many instances depancreatized animals with fatty liver displaying the other symptoms of lipocaic deficiency (decreased activity, loss of appetite, decreased excretion of dextrose and decreased insulin tolerance) have been restored to normal by the administration of an effective pancreas preparation and maintained so for several months, only to experience prompt development of fatty liver again and die when the lipocaic was discontinued.

CRITERIA OF LIPOCAIC DEFICIENCY

The symptoms and signs of lipocaic deficiency were described in large part in a previous paper¹³ and have been alluded to in the foregoing section. An erroneous impression has arisen somehow that the sole criterion of lipocaic deficiency employed in this laboratory has been the demonstration by histologic means of fat in a small section of liver taken by biopsy (Chaikoff and Kaplan,¹⁴ Aylward and Holt,¹⁵ Ivy and Crandall¹⁶). Indeed, Aylward and Holt stated

It may not be out of place, however, to point out that Dragstedt and his collaborators rested their case entirely upon histological evidence, which does not invariably give an accurate picture of the chemical state of the liver.

Because of this confusion, we should like to repeat here the criteria that have been employed both for the demonstration of lipocaic and for determining the activity of a pancreas extract under study.

In the final analysis the demonstration of lipocaic depends on the recognition that the depancreatized dog fed a mixed diet of protein, carbohydrate and fat is not restored to a normal state by the adequate

15 Aylward, F. X., and Holt, L. E. *J. Biol. Chem.* **121** 61, 1937.

16 Ivy, A. C., and Crandall, L. A., in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1938, vol. 7, p. 404.

administration of insulin and the external pancreatic secretion. The oral administration of pancreas or of a fat-free alcoholic extract of pancreas corrects the remaining deficiency, prevents the accumulation of abnormal amounts of fat in the liver and makes survival for a long period in a good nutritional state possible. In the assay of pancreas fractions for lipocaic, several animals, usually 3, were depancreatized and placed on a standard diet, and careful measurement was made of the amount of dextrose excreted daily and the insulin requirement. Commonly 20 to 30 units of regular insulin daily were required to keep the dextrose excretion under 10 Gm, although wide variations were found in different animals. A progressive decrease in dextrose excretion and a consequent decrease in insulin requirement were found to occur, so that after four to six weeks the animals might excrete less than 5 Gm of dextrose daily and receive only 2 to 5 units of insulin and even on these small doses display severe and even fatal hypoglycemic convulsions. Symptoms such as decreased activity, loss of appetite, apathy and some muscular weakness were usually apparent. A laparotomy was then done and the liver inspected. A marked fatty infiltration of the liver is unmistakable even on gross inspection, and moderate degrees of fatty change are readily appreciated. The liver is enlarged, bright yellow and friable. A biopsy specimen may be secured with little or no bleeding. Usually the fat appeared to be uniformly distributed through the liver, and a representative section was always chosen for the biopsy. In our first experiments histologic examination only was made of the biopsy specimen, but during the past two years this has been supplemented by chemical determination of the total lipid content. After the laparotomy and biopsy the animals were fed the test pancreas fraction and the material was concluded to contain an effective dose of lipocaic if the animals displayed clinical improvement (increase in weight, increase in appetite and increased activity), an increase in dextrose excretion (occasionally to as much as 20 to 60 Gm per day) and an increase in insulin requirement and tolerance (a return to the amount of insulin required immediately after pancreatectomy). This conclusion was always verified by a second laparotomy, inspection of the liver and biopsy. Since the previous report we have made use of two additional criteria, namely the bromsulphalein test of hepatic function (Goodpasture, Vermeulen, Donovan and Dragstedt¹⁷) and measurement of the concentration of the total blood lipids. In the presence of a fatty liver due to lipocaic deficiency the hepatic function is impaired, as indicated by abnormal retention of bromsulphalein, and the concentration of total lipids in the blood is reduced to about

17 Goodpasture, W. C., Vermeulen, C., Donovan, P. B., and Dragstedt, L. R. *Am. J. Physiol.* **124**: 642, 1938.

half the normal concentration. Both are returned to normal, usually within two weeks, by the oral administration of an adequate dose of lipocaine.

Criticism directed to our use of laparotomy, inspection and biopsy of the liver in these studies seems to us unwarranted. The most obvious defect in the depancreatized insulin-treated dog is the extreme fatty change in the liver. We are interested in determining the therapeutic effectiveness of various pancreatic extracts in this condition. It seems obvious, then, that the presence of fatty liver should be verified before the test is made, particularly since, as we have indicated, not all depancreatized dogs show it. It is true that determination of the amount of fatty infiltration in the liver by inspection and microscopic examination

TABLE 1—*Correlation Between the Estimation of Fat in the Liver by Histologic and by Chemical Methods*

No Fat*		Fat +		Fat ++		Fat +++		Fat +++ +	
Animal No	Fat, %	Animal No	Fat, %	Animal No	Fat, %	Animal No	Fat, %	Animal No	Fat, %
711	4.7	330	6.3	711	12.8	654	43.7	665	39.5
314	4.3	651	7.6	711	7.8	678	13.1	888	39.3
514	13.4	976	6.0	711	10.0	674	12.9	665	36.1
714	4.4	654	6.8	654	20.5	896	21.0	695	35.2
653	6.6	885	6.8	940	12.5	768	28.2	673	42.0
784	4.0	884	8.2	678	12.1	847	35.2	715	38.8
801	4.0	330	21.3	678	9.1	979	32.0	717	36.8
955	6.8	955	14.0	653	14.4	969	20.4	726	45.0
893	7.8	93	7.0	883	15.0	940	23.0	330	38.4
651	5.5	883	11.2	717	23.8	967	17.6	940	33.0
Average	6.15		9.54		13.8		24.71		38.41

* The normal liver contains considerable fat which is not visible in stained sections.

is not always accurate, especially when only slight changes exist, but then, of course, no conclusions can be drawn. Estimation of the degree of fatty infiltration in the liver by histologic methods is, however, more accurate than some physicians may have supposed. This is evident from inspection of table 1, in which are included data from biopsy of 50 livers in which independent histologic examination and chemical determination of fat content were made by two different observers. Sections were stained with scarlet red and the amount of fat present indicated by grades from zero to 4 plus. For the chemical determination of fat a portion of the fresh biopsy specimen was repeatedly extracted with alcohol and ether with the aid of a reflux condenser after being ground with sand. The solvent was then removed by evaporation and the remaining fat weighed. Individual variations of considerable magnitude in the results obtained by the two methods may be found, but in general the correlation was satisfactory for the purpose, particularly when considerable amounts of fat were present.

That variations in the distribution of fat within a given fatty liver exist has been found by Chaikoff and Kaplan¹⁸ (1937) and is also illustrated by data from our own experiments (table 2). In our experience, however, these variations were so slight as to be of no consequence in interpreting the effect of the deprivation of lipocaic on therapy.

INCIDENCE OF FATTY CHANGES IN THE LIVER IN DEPANCREATIZED DOGS TREATED WITH REGULAR INSULIN AND WITH PROTAMINE ZINC INSULIN

In discussing the papers of Dragstedt, Van Plohaska and Harms, Wilder and Wilbur¹⁹ (1937) made the suggestion

That the discontinuous action of insulin, when readily soluble (regular) insulin is given by infrequent injection, may be responsible for the hepatic degeneration of depancreatized animals and that pancreas and derivatives of pancreas given by

TABLE 2—*Distribution of Fat as Determined by Chemical Analysis in Different Portions of the Liver of Depancreatized Dogs (Specimens Secured at Autopsy)*

Animal No	Lobe 1 Fat, %	Lobe 2 Fat, %	Lobe 3 Fat, %	Lobe 4 Fat, %	Lobe 5 Fat, %	Average
976	5.7	6.1	6.2	6.8		6.2
678	9.8	9.7	9.1	9.1	10.8	9.7
276	46.3	42.5	43.4	41.1		43.3
955	6.1	6.8	6.4	6.5		6.45
35	24.6	24.2	23.8	29.8	26.6	25.8
899	26.2	25.6	26.1	23.7		25.4
320	20.2	17.9	20.5	20.1		19.7
967	4.6	5.3	5.0	4.5		4.85
95	22.0	29.3				25.6

mouth could owe their curative and preventive properties to some action whereby a more continuous insulin effect is maintained.

Such an explanation, if correct, would simplify the situation considerably. The available data from our laboratory, however, indicate that the incidence of fatty infiltration of the liver in depancreatized dogs treated with protamine zinc insulin²⁰ is just as great as in those treated with regular insulin. From Jan 1, 1935, to Jan 1, 1937, the depancreatized animals in our laboratory were treated with regular insulin. From Jan 1, 1937 to May 1, 1938, protamine zinc insulin was used, and from this time to the present we have used regular insulin. In all, 154 animals have been depancreatized. Of these, fatty changes in the liver which could be attributed to lipocaic deficiency developed in 116. In 13 the liver remained normal, although these were observed long enough for a fatty liver to appear within the usual time. Twenty-five of the animals died

18 Chaikoff, I. L., and Kaplan, A. J. *Biol. Chem.* **119**: 423, 1937.

19 Wilder, R. M., and Wilbur, D. L. *Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions*, *Arch. Int. Med.* **59**: 329 (Feb.) 1937.

20 All insulin used in this study was furnished by Eli Lilly & Co.

soon after the operation or were used for other types of experiment, so that data concerning the appearance of the fatty changes in these are not reliable. Thus, in our experience fatty changes in the liver which may be attributed to lipocais deficiency occur in about 90 per cent of insulin-treated depancreatized dogs. Data with respect to the extent of the fatty infiltration in the liver and the time of onset were obtained by several criteria of lipocais deficiency, namely (1) rate of decrease of dextrose excretion, (2) rate of decrease in insulin requirement or tolerance, (3) loss of appetite and decreased activity, (4) hepatic function determined by the bromsulphalein test and (5) results of microscopic and chemical examination of a representative section after laparotomy, inspection of the liver and removal. For 31 animals given regular insulin on which complete data were secured, biopsy specimens of the liver were obtained an average of thirty-six days after pancreatectomy. Nine of these showed an average of 37.3 per cent (4 plus), 12, 22.1 per cent (3 plus), 9, 14.1 per cent (2 plus), and 1, 11 per cent (1 plus) fat in the liver. For 20 animals given protamine zinc insulin on which complete data were obtained, biopsy specimens of the liver were secured an average of thirty-six days after pancreatectomy. Four of these showed an average of 38.3 per cent (4 plus), 10, 24.4 per cent (3 plus), 3, 13.4 per cent (2 plus), and 3, 9.5 per cent (1 plus) fat in the liver. It is thus evident that there is no significant difference between the animals given regular insulin and those given protamine zinc insulin in respect to the time of onset of the fatty changes in the liver or their severity.

The use of protamine zinc insulin provides better control of the diabetes in the sense that a constant absorption of small amounts produces a state more nearly simulating normal than is secured by the use of regular or soluble insulin. The same incidence of fatty liver in the two series is further evidence that the type of fatty infiltration involved here is not due to poor control of the diabetes. It is difficult to avoid hypoglycemic convulsions when protamine zinc insulin is employed in the treatment of experimental diabetes, largely because of variations in the amount of food ingested by the animal from day to day and of a cumulative effect of the slowly absorbed insulin. These convulsions are much more difficult to treat than those occurring with regular insulin therapy and occasion a considerable mortality. For this reason we have returned to the use of regular or soluble insulin.

EFFECT OF THE ORAL ADMINISTRATION OF INSULIN ON THE DEVELOPMENT OF FATTY LIVER IN THE DEPANCREATIZED DOG

Can the beneficial effect attributed to lipocais be accounted for on the basis of an unknown action of insulin given by mouth? Will the presence of insulin in the intestine prevent fatty infiltration of the liver in

depancreatized dogs? In our first preparations of lipocaic varying amounts of insulin were undoubtedly present. For these reasons the following experiment was performed. On Feb 3, 1936, an animal was submitted to total pancreatectomy and placed on a diet of bread, whole milk, meat, cod liver oil and brewers' yeast. Regular insulin was given. On Feb 29, 1936, a laparotomy was done and the liver seen to be fatty on gross and microscopic inspection, a section contained 32 per cent fat by chemical examination. An adequate dose of lipocaic was then added to the previous diet, and on March 29, 1936, a third laparotomy was done. The liver was found to be normal. Fifty milligrams of dried powdered insulin, containing 1,200 units, was then substituted for the lipocaic and fed with the regular diet for thirty-six days. On May 4, 1936, a fourth laparotomy was done and the liver was found again to be fatty (38.4 per cent). On May 9, 1936, the animal died, and autopsy confirmed the extensive fatty infiltration and degeneration in the liver. The results of this one experiment were so definite and the amount of insulin used so large that it seemed unnecessary to repeat it. It is interesting that the oral administration of this tremendous dose of insulin had no effect whatever on the dextrose excretion, and it is equally apparent that it had no beneficial effect on the fatty infiltration in the liver.

EFFECT OF CHOLINE AND BETAINES HYDROCHLORIDE ON THE FATTY INFILTRATION OF THE LIVER IN DEPANCREATIZED DOGS

MacLean and Best²¹ (1934) reported that the oral administration of choline in doses varying from 1.5 to 2.25 Gm per day was effective in relieving fatty liver in depancreatized dogs. This observation was confirmed by Van Prohaska, Dragstedt and Harms¹⁸ (1936), who reported a beneficial effect obtained with as little as 1 Gm of choline daily, but that smaller doses were ineffective. Since this report we have given choline to 6 additional depancreatized dogs, with the following results. Four of the animals were placed on a diet of bread, milk, meat, cod liver oil and brewers' yeast, and the glycosuria was partially controlled with regular insulin. One animal, whose liver on biopsy showed fat, 2 plus (13.4 per cent), was given 200 mg of choline daily for thirty days, after which a second biopsy disclosed an increase in the amount of fat (3 plus, or 22.2 per cent). This animal was then given 1 Gm of a fat-free extract of pancreas for twenty-nine days, and at that time the liver was found to be normal. A second animal with a very fatty (4 plus, or 37 per cent) liver was given 500 mg of choline daily for ten days, after which it died of hypoglycemic convulsions. The fat

21 MacLean, D. L., and Best, C. H. *Brit J Exper Path* **15** 193, 1934

content of the liver was unchanged. A third animal with a very fatty (4 plus, or 33 per cent) liver was given 700 mg of choline daily for twenty-eight days, after which a second laparotomy and biopsy disclosed an increase in the fat content to 43 per cent. A fourth animal with a moderately fatty (2 plus, or 14.4 per cent) liver was given 1 Gm of choline daily for twenty-nine days, after which it died of pneumonia. There was no improvement in the liver. The remaining 2 animals were given a casein diet in addition to the choline and will be considered in the subsequent section.

Most of the observations on the lipotropic action of betaine hydrochloride have been made on dietary fatty liver in rats, and for that reason it seemed advisable to secure additional evidence with respect to its effect on fatty liver in depancreatized dogs. We have given betaine hydrochloride to 4 depancreatized dogs proved to have fatty liver by laparotomy, inspection and biopsy. The results are as follows. All the animals were fed bread, meat, milk, cod liver oil and yeast and given regular insulin. One animal, whose liver at biopsy was fatty (3 plus) was given 2 Gm of betaine hydrochloride daily for seven days, after which severe convulsions developed and it was electrocuted. The fat content of the liver was unchanged (3 plus). In a second animal, whose liver became fatty (2 plus) in thirty-eight days after pancreatectomy, the condition was controlled for four months by a preparation of lipocain, and at the end of this time the liver was only slightly fatty (1 plus). The animal was then given 2 Gm of betaine hydrochloride daily for forty-three days, after which laparotomy and biopsy disclosed an increase in the liver fat (3 plus). The gradual decrease in dextrose excretion and the reduction in insulin requirement also indicated that this amount of betaine hydrochloride was ineffective. A third animal, whose liver was moderately fatty (2 plus, or 12 per cent), was given 3 Gm of betaine hydrochloride daily for twenty-one days. After this time the various criteria of lipocain deficiency indicated that the condition of the animal was getting worse, and biopsy of the liver indicated an increased fat content (17 per cent). The fourth animal was found to have a moderately fatty liver (2 plus, or 14 per cent) when examined eighty-nine days after pancreatectomy, 3 Gm of betaine hydrochloride daily was then given for twenty-four days, with definite clinical improvement and decrease in the liver fat to 1 plus. The same dose was continued then for sixty-five days, after which the liver was found to be entirely normal (fat content, 6.3 per cent). The administration of betaine hydrochloride was then stopped. Within two weeks the sugar excretion decreased markedly, and the dose of insulin had to be reduced. Two months after medication was stopped, the bromsulphalein test revealed moderate impairment of hepatic function, and biopsy after three months revealed

a definite return of fat in the liver, to 3 plus, or 21 per cent. At this time the blood lipids had decreased to 450 mg per hundred cubic centimeters, or less than half the normal value.

EFFECT OF CASEIN AND OF VARIATIONS IN DIET ON THE FATTY INFILTRATION OF THE LIVER IN PANCREATIZED DOGS

In 1932 Best, Hershey and Huntsman^{12d} demonstrated that a diet of mixed grain and 40 per cent beef fat would produce a marked fatty infiltration in the liver of normal rats. This type of dietary fatty liver was found to be prevented by the addition of small amounts of choline to the food (Best and Huntsman,^{12e} Best and Ridout,^{12f} Best, Channon and Ridout^{12a}). Casein was later found to exert a similar lipotropic effect (Best and Huntsman,²² Channon and Wilkinson,²³ Beeston, Channon and Wilkinson²⁴). Best, Grant and Ridout²⁵ (1936) produced fatty liver in rats by feeding a diet containing 40 per cent fat and 10 per cent casein. When the percentage of casein was raised to 30 or above, no fat accumulated in the liver. The fatty liver produced by the low casein, high fat diet could be prevented by the addition of 10 mg of choline per rat daily. The authors suggested that 1 Gm of casein exerts an effect comparable to that of 5 or 6 mg of choline. In a similar experiment Channon, Loach, Loizides, Manifold and Soliman²⁶ (1938) estimated that 1 Gm of caseinogen has an effect equivalent to that of 7 to 8 mg of choline.

In 1937 MacKay²⁷ reported that an extract of pancreas prepared as described by Dragstedt, Van Prohaska and Harms was effective in preventing and in curing the type of fatty infiltration of the liver that occurs in rats on a low protein, high fat diet. This finding was confirmed by Aylward and Holt¹⁵ (1937) and by Best and Ridout²⁸ (1938). Both groups, however, concluded that the effect of the pancreas extract in this connection could be accounted for on the basis of its choline and protein content. MacKay and Barnes²⁹ (1938) came to a similar conclusion. On the other hand, Channon, Loach and Tristram³⁰

22 Best, C. H., and Huntsman, M. E. *J. Physiol.* **83** 255, 1935.

23 Channon, H. J., and Wilkinson, H. *Biochem. J.* **29** 350, 1935.

24 Beeston, A. W., Channon, H. J., and Wilkinson, H. *Biochem. J.* **29** 2659, 1935.

25 Best, C. H., Grant, R., and Ridout, J. H. *J. Physiol.* **86** 337, 1936.

26 Channon, H. J., Loach, J. V., Loizides, P. A., Manifold, M. C., and Soliman, G. *Biochem. J.* **32** 976, 1938.

27 MacKay, E. M. *Am. J. Physiol.* **119** 783, 1937.

28 Best, C. H., and Ridout, J. H. *Am. J. Physiol.* **122** 67, 1938.

29 MacKay, E. M., and Barnes, R. H. *Proc. Soc. Exper. Biol. & Med.* **38** 410, 1938.

30 Channon, H. J., Loach, J. V., and Tristram, G. R. *Biochem. J.* **32** 1332, 1938.

(1938), using similar methods, came to exactly the opposite conclusion. They stated

Eight assays of the activity of the five pancreatic extracts used were made, all of them showed the extracts to possess an ability to prevent fat deposition in the liver greater than could be attributed to their content of choline. The average value for this non-choline activity was equivalent to that of 426 mg of choline per 100 Gm pancreas while the choline present in the extracts accounted for only one-third of their activity. The non-choline activity is not accounted for by the protein content of the extracts and it is concluded that there exists in pancreas a substance other than choline which is involved in fat deposition in the liver.

We have made no observations on the effect of lipocaic on dietary fatty liver in rats. It should perhaps be pointed out, however, that fatty infiltration of the liver in animals may be produced in a great variety of ways and the significance of each state not be the same. A failure to demonstrate a lipotropic effect of lipocaic on dietary fatty liver in otherwise normal rats when the pancreas is intact can hardly be advanced as evidence against its effect on a specific defect in the depancreatized dog until it is clearly demonstrated that the disturbance in each case is the same. The positive findings of Professor Channon are therefore of special interest and significance.

In view, however, of the clearcut demonstration of the marked effect which choline and certain proteins, notably casein, have on dietary fatty liver in rats, it seemed important to us to secure some evidence with respect to the effect of these substances both singly and in combination on the depancreatized dog.

The stock diet most commonly used in this laboratory has been made up of white bread, whole milk, beef muscle and bone meal, plus small amounts of cod liver oil and brewers' yeast. The fat content of this diet is approximately 25 per cent. In our experience dogs take this diet more readily than others and may be maintained in excellent nutrition in laboratory cages for four or five years. In our first experiments³ yeast and cod liver oil were not added to the diet. Chaikoff and Kaplan¹⁴ (1937) have suggested that the early appearance of fatty liver and the relatively short survival period of depancreatized dogs fed this diet may be due to vitamin deficiency. The prompt recovery of these animals when given a fat-free alcoholic extract of pancreas, however, speaks against this view. It has seemed wise to add the vitamin supplements, nevertheless, although to date such addition has not altered the picture appreciably. The suggestion of Himwich³¹ (1938) that failure to secure long survival of depancreatized dogs fed this diet is due to inadequate absorption does not seem valid in view of the fact pointed out in our previous report¹³ that the addition of large amounts of fresh active

31 Himwich, H. E., in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1938, vol. 7, p. 143.

pancreatic juice, which improves digestion and absorption, nevertheless does not delay the appearance of fatty liver or prolong life. Indeed, in view of the results to be reported later, it seems more likely that the better absorption of fat secured by the feeding of pancreatic juice has led to a more rapid accumulation of fat in the liver and to a decrease in the period of survival.

In the following experiments three diet mixtures have been employed, the compositions of which are indicated in table 3. Cowgill's³² casein III diet was selected because in the experience of that investigator the formula has been found to be balanced and adequate for dogs. It was

TABLE 3—*Composition of Special Diets Fed to Depancreatized Dogs*

(1) Cowgill's (1936) Casein III Diet (Modified)		Percentage
Casein, commercial (12.7% N)		38.45
Sucrose		27.45
Bone ash		2.45
Salt mixture*		1.22
Lard		22.03
Cod liver oil		1.87
Brewers' yeast		6.53
(2) High Casein, Low Fat Diet		
Casein		45
Sucrose		45
Bone ash		3
Salt mixture*		1
Cod liver oil		2
Brewers' yeast		4
(3) Low Casein, High Fat Diet		
Casein		26.6
Sucrose		19.0
Salt mixture*		1.3
Bone ash		2.6
Lard		44.1
Cod liver oil		2.0
Brewers' yeast		4.4

* Formula for the salt mixture: sodium chloride, 25%; potassium chloride, 25%; calcium lactate, 22.5%; magnesium citrate, 22%; ferric citrate (finely ground), 5%; potassium iodide 0.5%.

fed to 7 depancreatized dogs, usually with the addition of 400 cc of milk to make the mixture more palatable, and from 100 to 300 cc of pancreatic juice daily. One dog failed to show a fatty liver and remained in good condition. The other 6, however, were no different from the animals on the bread, meat and milk diet. The fatty infiltration in the liver appeared just as rapidly and was equally severe. In 1 additional animal the effect of choline was investigated. This animal was depancreatized and placed on a diet of bread, meat, milk, bone meal, brewers' yeast, cod liver oil and 200 cc of pancreatic juice daily. Laparotomy and biopsy at the end of thirty days revealed a fatty liver graded 2 plus. Cowgill's casein III diet was then given and a potent preparation of

32 Cowgill, G. R. Personal communication to the authors.

lipocaic added. Biopsy in twenty-eight days revealed a normal liver. One gram of choline daily was then substituted for the lipocaic and the casein III diet continued as before. Laparotomy and biopsy in sixteen days revealed a reaccumulation of fat in the liver, graded 4 plus.

The low casein, high fat diet was fed to 4 depancreatized dogs. These animals were also given supplementary feedings of fresh pancreatic juice daily in amounts of from 100 to 300 cc. Marked fatty liver developed in 3, in each somewhat sooner than in animals fed the stock diet. An abbreviated protocol for the fourth animal is supplied, because it illustrates a beneficial result obtained with choline.

Dog 663—On July 27, 1936, pancreatectomy was done and a diet of bread, milk, meat, bone meal, yeast and cod liver oil given, with regular insulin and 100 cc of pancreatic juice daily. On September 8 biopsy showed 3 plus fat in the liver. From Sept 8 to Jan 4, 1937, the aforementioned diet was continued, with addition of a potent preparation of lipocaic. On January 4 laparotomy and biopsy showed the liver normal. From January 5 to 19 Cowgill's casein III diet, 160 Gm, plus 400 cc of milk and 200 cc of pancreatic juice was given daily. From January 19 to February 8 a low casein, high fat diet plus 400 cc of milk and 200 cc of pancreatic juice was given daily. On February 8 biopsy showed 4 plus fat in the liver. From February 10 to March 9 a low casein, high fat diet plus milk and pancreatic juice and 2 Gm of choline was given daily. On March 9 biopsy showed the liver normal.

The high casein, low fat diet was fed to 3 depancreatized dogs. The effects are indicated in the following abbreviated protocols.

Dog 269—On March 22, 1937, pancreatectomy was done, and a diet of bread, meat, milk and vitamin supplements with pancreatic juice, 100 cc, and protamine zinc insulin was given. On April 23 biopsy showed 3 plus fat in the liver. From that date to May 2 the high casein, low fat diet with pancreatic juice but no milk was given. On May 2 the dog died in convulsions (presumably hypoglycemic). Autopsy showed the liver normal.

Dog 104—On Jan 25, 1937, pancreatectomy was done, and a diet of bread, milk, meat and vitamin supplements was given, with 70 cc of pancreatic juice daily and protamine zinc insulin. On March 2 biopsy showed 1 plus fat in the liver. From March 2 to April 9 the high casein, low fat diet plus 400 cc of milk and 50 cc of pancreatic juice was given. On April 9 biopsy showed 1 plus fat in the liver. From April 9 to 19 a diet of bread, meat, milk and vitamin supplements was used. On April 19 the animal died of hypoglycemic convulsions. Autopsy showed 3 plus fat in the liver.

(A beneficial effect of the high casein, low fat diet on this animal was indicated by the increased dextrose excretion and increased insulin tolerance during this period, with no increase in liver fat. A blood lipid content of 420 mg per hundred cubic centimeters on February 4, of 520 mg on February 17 and of 880 mg on March 17 confirmed this view.)

Dog 47—On Jan 22, 1937, pancreatectomy was done and a diet of bread, meat, milk and vitamin supplements given, with 80 cc of pancreatic juice daily and protamine zinc insulin. On March 2 biopsy showed 2 plus fat in the liver. From March 2 to April 9 the high casein, low fat diet plus 400 cc of milk and 100 cc.

of pancreatic juice was given. On April 9 biopsy showed the liver normal. Dextrose excretion and insulin tolerance were increased. From that date to August 12 the high casein, low fat diet plus 100 cc of pancreatic juice but no milk was given. On August 12 biopsy showed 2 plus fat in the liver.

The additional evidence secured in these experiments indicates that approximately 2 Gm of choline per day over and above that contained in the diet is required to prevent or relieve the fatty infiltration of the liver that occurs in depancreatized dogs. This agrees with the findings of Rall, Rubin and Present³³ (1938), who reported that even this amount may not be uniformly effective in preventing some degree of fatty infiltration. It seems equally clear that a high fat, low protein diet facilitates, and a low fat, high protein diet delays, the appearance of fat in the liver in these animals when pancreatic juice is also provided to improve the digestion and absorption of the food. It is probable that the proportion of fat in the diet is of greater significance in this connection than the amount or quality of protein and its possible lipotropic action. Thus Cowgill's casein III diet, which contained 38 per cent casein and 24 per cent fat, did not delay the appearance of fat in the liver more than the bread, meat and milk diet, which contained 25 per cent fat. One gram of choline daily in addition to the diet containing 38 per cent casein did not prevent the development of fatty liver in an animal proved to be susceptible and in which on a previous trial 2 Gm of a fat-free alcoholic extract of pancreas was effective. When the casein level was reduced to 27 per cent and the fat raised to 46 per cent, fat deposition in the liver was definitely accelerated. Although more data are obviously required, the diet high in casein and low in fat did definitely retard the appearance of fat in the liver and improve the clinical condition of the animals. It seems likely that such a diet may lessen the need for lipocaic, and this, if true, would be of great significance with respect to the function of this substance. In this connection it is of interest that the diet used by Chaikoff and Kaplan¹⁴ (1937), on which an unusually long survival was secured, contained relatively little fat, only that present in raw lean beef apparently being ingested.

SOME PREPARATIONS OF LIPOCAIC AND THEIR CHOLINE CONTENT

In the initial experiments reported by Dragstedt, Van Prohaska and Haims³ (1936) the activity of pancreas was found to be retained in alcoholic extracts freed from fat by extraction with ether. In view of the fact that insulin is obtained by a somewhat similar procedure, whereas the beneficial action of pancreas in this particular is not exerted by insulin, it seemed desirable to determine, if possible, where lipocaic

³³ Rall, E. P., Rubin, S. H., and Present, C. H. *Am J Physiol* **122** 43, 1938.

was lost in the extraction of pancreas for the preparation of insulin. In this attempt we secured the help of Drs G H A Clowes and George B Walden, of Eli Lilly & Co, who prepared numerous pancreatic fractions. In the preparation of insulin, fresh pancreas may be extracted with alcohol acidified with sulfuric acid. As near as we can estimate by our methods, approximately three fourths of the lipocaic in the pancreas appeared in the acid alcohol and one fourth remained in the residue. The dried residue was administered to 8 depancreatized dogs and in 3 of these was found to be effective in a dose of 10 to 20 Gm per day. Hot water extracts of this pancreatic residue were given to 5 depancreatized dogs and were found to be effective in a dose of 3 to 4 Gm of dried material. These extracts were examined by Dr Edward Eagle and found to contain between 3 and 4 mg of free choline per gram of dried substance. The estimations of choline were made by the method of Ambo and Aoki,³⁴ as modified by Eagle. Dr Eagle also made the subsequent determinations of choline in the pancreatic extracts described in this paper. The acid-alcohol extract of the whole pancreas may be partially evaporated to drive off the alcohol and the remaining acid-water solution concentrated by evaporation and chilled and the fat skimmed off. The addition of a mixture of strong alcohol and ether to the preparation in the acid-water phase results in the formation of a precipitate. This, when dried, has been found to be effective in a dose of 0.75 to 1.5 Gm per day. This extract was found to contain 0.131 mg of choline per gram of dried substance. In the acid-water phase of the insulin-forming procedure the substance may be concentrated by evaporation and raised to 80 per cent alcohol concentration by the addition of strong alcohol. A precipitate relatively free from insulin forms and has been found to contain an effective dose of lipocaic in from 2 to 3 Gm of dried substance. Examination of three different preparations revealed less than 1 mg (0.604, 0.209 and 0.314 mg) of choline per gram of extract. These three preparations were dialyzed against distilled water through a celloidin membrane for from two to six weeks. The non-dialyzable fraction revealed the characteristic activity of lipocaic, whereas the dialyzate was found to be inert. If in the acid-water phase of the insulin extraction the substance is saturated with ammonium sulfate or with sodium chloride, both insulin and lipocaic may be thrown out as a precipitate. In the further steps in the preparation of insulin it seems probable that lipocaic is lost, owing to the fact that insulin is soluble in the higher concentrations of alcohol whereas lipocaic seems to be insoluble in alcohol of over 70 per cent concentration under the conditions of our experiments.

As noted in the previous section, the conclusion that the lipotropic effect of pancreas can be accounted for on the basis of its choline or

34 Ambo and Aoki. *Tr Jap Path Soc* **21** 171, 1931.

choline plus protein content has been based almost entirely on experiments on the type of fatty infiltration of the liver that occurs in normal rats fed a diet low in protein and rich in fat. The pancreas in these animals is intact, and it would seem reasonable to expect that the "factors of safety" involved in its function should be adequate to meet rather wide variations in dietary composition without a defect similar to that which obtains when the pancreas is removed resulting. While it may be true that the fatty liver produced by diet in the rat is the same as that produced by depancreatizing the dog, it would seem unwise, in the present state of knowledge, to apply conclusions derived in the former case to the specific defect present in the latter.

The evidence that choline is not the substance in pancreas which accounts for its beneficial action in preventing and relieving fatty infiltration of the liver in the depancreatized dog and in permitting the animal to survive for a long period when treated with adequate insulin also may be summarized as follows:

1 It requires approximately 2 Gm. of choline per day over and above that present in the diet to exert this beneficial effect, whereas 100 Gm. of pancreas, which is an effective dose, contains only about 250 mg. of choline.

2 Liver and brain, which contain as much or more choline exert no beneficial effect.

3 When extracts of pancreas are made, the active substance appears in the fat-free alcoholic extracts, whereas the ether-soluble fractions, which contain practically all the lecithin of the pancreas and accordingly almost all the choline, are inert.

4 It has been possible to secure fat-free extracts of pancreas effective in a dose of 1 to 2 Gm. of dried substance per day and containing not more than a few milligrams of choline per gram of dried substance.

SUMMARY AND CONCLUSIONS

The demonstration that lipocaic is an internal secretion of the pancreas depends on the recognition that the depancreatized dog fed on a mixed diet of protein, carbohydrate and fat is not restored to a normal state by the adequate administration of insulin and pancreatic juice, and that the remaining deficiency is corrected by the oral administration of pancreas or of certain extracts of pancreas but not of other organs.

Two types of fatty infiltration of the liver occur both in diabetes mellitus and in pancreatic diabetes. One type is due to poor control of the diabetes by inadequate administration of insulin and is characterized by a normal or high concentration of the blood lipids and acidosis and is relieved by better insulin therapy. The second type is due to

lipocaic deficiency and is characterized by a low concentration of the blood lipids, impaired hepatic function and decreased dextrose excretion and insulin sensitivity and is relieved by lipocaic therapy but not by insulin

In 92 per cent of 154 depancreatized dogs in our laboratory fatty infiltration of the liver developed, in the remaining 8 per cent the liver remained normal

All of a series of 12 depancreatized dogs that were fed a mixed diet of protein, carbohydrate and fat and treated with insulin but given no supplement other than pancreatic juice died with fatty liver within three months

For the assay of a pancreas fraction for lipocaic, it is suggested that a minimum of 3 depancreatized dogs be placed on a mixed diet of carbohydrate, protein and rather liberal amounts of fat and given sufficient insulin to permit a urinary excretion of dextrose of not more than 5 Gm per day. Lipocaic deficiency may be concluded to be present at the end of four to six weeks in the presence of the following symptoms and findings: decrease in appetite and activity, decrease in dextrose excretion, decrease in insulin requirement to 5 units or less per day with occasional hypoglycemic convulsions on this dose, 10 to 20 per cent retention of bromsulphalein twenty minutes after the intravenous injection of the dye and decrease in the concentration of the blood lipids to levels of 500 to 300 mg per hundred cubic centimeters—all to be confirmed by laparotomy, inspection of the liver and removal of a representative section for microscopic and chemical examination. That the dose of lipocaic is adequate may be concluded after administration of the test fraction for four to six weeks by disappearance of these abnormalities, checked again by laparotomy, inspection and biopsy of the liver

The distribution of fat in the liver in depancreatized dogs is found to be sufficiently uniform to justify attaching definite significance to the detection of fat in a single biopsy specimen

A comparison of the estimation of fat in the liver by histologic and by chemical methods is given

Better control of the diabetes by the use of protamine zinc insulin does not delay or decrease the incidence or severity of fatty infiltration of the liver in depancreatized dogs

The oral administration of 1,200 units of insulin daily for thirty-six days did not affect the onset or extent of fatty changes in the liver of a depancreatized dog

The oral administration of 3 Gm of betaine hydrochloride daily was found to be effective in relieving fatty liver in depancreatized dogs, but smaller doses, such as 2 Gm, were ineffective

At least 2 Gm of choline daily over and above the amount present in the diet is required to relieve fatty liver in depancreatized dogs. One gram of choline daily in addition to a diet containing 38 per cent casein did not prevent the development of typical fatty liver.

The substitution of casein as the source of protein in the diet of the depancreatized dog does not prevent or delay the appearance of fatty liver.

High fat, low protein diets accelerate, and low fat, high protein diets delay, the appearance of fatty liver in depancreatized dogs.

It has been possible to secure fat-free alcoholic extracts of pancreas containing an adequate dose of lipocair in 1 Gm of the dried substance and containing not more than a few milligrams of choline per gram.

It seems probable that lipocair is removed from the usual preparation of insulin, since insulin is soluble and lipocair is insoluble in alcohol when the concentration reaches 90 per cent.

STRUCTURAL CHANGES IN THE LUNGS OF DRUG ADDICTS

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In reviewing thoracic roentgenograms taken routinely of several thousand drug addicts admitted to the Riker's Island Hospital in the past few years, a number of varied and interesting findings were noticed. These, as will be shown later, appeared to be entirely at variance with the patients' complaints and their clinical course. They also varied in intensity almost directly with the period during which the drugs had been used.

The addicts were subjected to a six day reduction regimen immediately on their admission to the hospital. Roentgen examination of almost all of them was done on the fourth or fifth day after the commencement of the period of withdrawal of the drug. This usually corresponds to the time in which symptoms due to withdrawal begin to wane and the patient feels comparatively comfortable. Roentgen examination of a few was done during the height of these symptoms, which occurs usually on the second day after the beginning of the reduction period. In the latter group the pulmonary changes were most pronounced.

Before any conclusions were drawn from observations as to the relation between the use of drugs such as cocaine and opium and its alkaloids and their possible effects on parenchymal pulmonary changes, a search of the literature was made for the purposes of studying the pharmacology and the physiology of the drugs in question and of establishing, if possible, physiologic principles on which the clinical observations might be based. Although this search did not disclose similar observations, it provided me with important clinical experimental data which substantiate my own findings and the conclusions I intend to set forth.

ANALYSIS OF CLINICAL DATA

During the past fifteen months roentgen examination of the chests of 674 male addicts was done, in most instances after and in a few during the height of the symptoms caused by withdrawal of the drug. One hundred ambulatory drug addicts were studied for the purpose

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of determining the status of the upper respiratory tract. The investigation consisted of routine examinations of the sinuses by means of transillumination, roentgen examination of the sinuses was done in 50 cases. The teeth, tonsils, pharynxes and nasal septums were inspected. In 80 other cases the changes were observed accidentally in the hospital after the development of acute illness.

The addicts may be divided into two classes (1) those who entered the hospital voluntarily and (2) those who were imprisoned after conviction for crimes not necessarily connected with the use of drugs.

TABLE 1—*Summary of Clinical Data*

Number of patients	674
Age, years	
Youngest	17
Oldest	62
Average	39
Period of addiction	
Shortest period	Three months
Longest period	Thirty nine years
Average	Eighteen years
Kind of Drugs Employed	
Heroin, opium, morphine, cocaine, laudanum, hashish, cannabis, sodium amytal and pentobarbital sodium	
Methods of introduction	
Subcutaneous, intravenous, inhalation and oral	
Period of Observation	
From the third to the sixth day of the withdrawal period	
A few during the height of the withdrawal symptoms	
Method of treatment	
All patients were treated by progressive withdrawal over a six day period	

Most of them had apparently acquired the habit during adolescence and had continued it consistently except for brief intermissions which usually occurred because of imprisonment or lack of funds. After each of these intervals the habit would be resumed more relentlessly. The youngest addict was 17 years old, the oldest was 62 and the average age was 39. At the time of observation the duration of addiction ranged, according to the addicts, from three months to thirty-nine years. The average was eighteen years. Almost all of the patients had taken more than one drug at some time. Heroin (diacetylmorphine) was the drug most commonly employed. This was partly due to the fact that it is more accessible and, according to the addicts, less expensive. Opium and its derivative morphine were next in order among the drugs.

used Cocaine, contrary to popular conception, was used comparatively less than the others. A few employed so-called "bombshells" or "speed balls," which usually contained a mixture of morphine and cocaine and were taken subcutaneously. In addition, some admitted having used hashish, cannabis, laudanum and marijuana (cannabis). A few supplemented the drugs mentioned with sedatives, such as sodium amytal and pentobarbital sodium. One prisoner, a Chinese, acquired, while in prison, the probably unique habit of smoking powered aspirin (acetylsalicylic acid). This he readily secured from the attendants by complaining of constant headaches. When given phenyl salicylate instead, he showed an uncanny instinct in recognizing that it was not aspirin.

Most of the drugs were taken subcutaneously. Other routes, in the order of frequency: (1) intravenous injection (addicts using this method are the so-called "main line shooters"), (2) smoking of opium and (3) inhalation, usually of cocaine. The majority of the patients had employed combinations of drugs as well as more than one avenue of introduction.

The addicts represented every stratum in the social scale. However, the majority belonged to the lower classes. It must be remembered that most drug addicts display psychopathic trends and are particularly giving to lying. Information elicited from them, therefore, is not necessarily accurate.

A definite routine was followed in all cases. Immediately on the patient's admission to the hospital a brief but pertinent history was elicited with reference to age, past illnesses, duration of the habit, periods of interruption and kind or kinds of drugs used. The withdrawal treatment to which the addicts were subjected consisted of subcutaneous injections of progressively diminished quantities of morphine sulfate. The entire withdrawal treatment lasted only six days. The usual symptoms were observed and were regarded with equanimity. However, when other signs and symptoms occurred, as they frequently did, they were treated accordingly. At the end of the six day period each patient was automatically transferred to another part of the hospital to receive custodial care and to serve the usual sentence of one hundred days.

ROENTGEN FINDINGS

Of the 674 patients the thoracic roentgenograms of only 92 (13.5 per cent) were entirely normal. The remainder (86.5 per cent) showed various abnormalities. The commonest abnormality consisted of pulmonary changes characteristic of hypertrophic emphysema,¹ i. e.,

1 Assmann, H. *Die klinische Roentgendiagnostik der inneren Erkrankungen*, ed 5, Leipzig, F. C. W. Vogel, 1932. Sante, L. R. *The Chest Roentgenologically Considered*, New York, Paul B. Hoeber, Inc., 1930.

voluminous lung fields, prominent hilar shadows, diffuse, increased vascular markings (due to peribronchial and perivascular thickening as well as to fine interstitial fibrosis), an outline, usually of the right interlobar fissure, between the upper and middle lobes, obliteration of one or both costophrenic sinuses, and tenting and occasionally distortion of one or both diaphragmatic domes (fig 1) The group in which these changes were present numbered 207 patients (30.7 per cent), most of whom had used drugs from fifteen to twenty years. Another group, of 94 patients (13.94 per cent), merely showed signs of emphysema (fig 2) without generalized increase in pulmonary markings.²

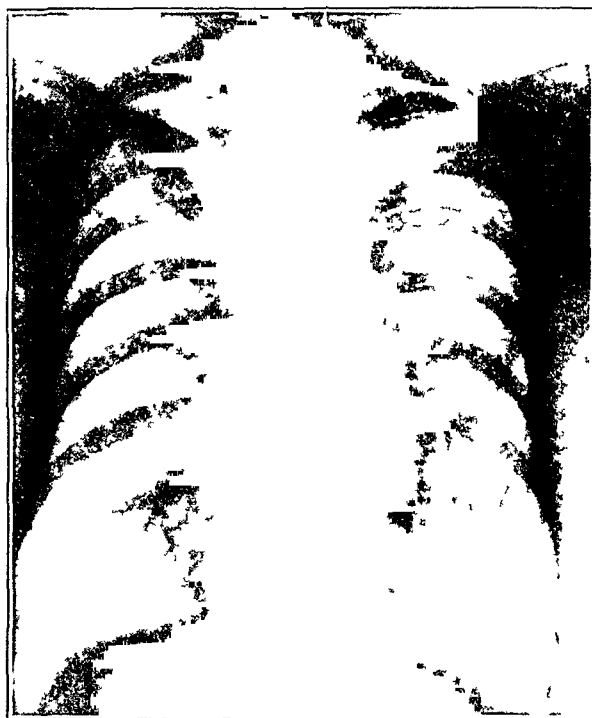


Fig 1—Roentgenogram of the chest of a drug addict

In a small group there were increased markings with slight signs or no signs of emphysema. These patients numbered 32 (4.74 per cent). The addicts in this group had, according to their history, a short period of addiction, from three months to five years (fig 3).

The remainder of the addicts (149, or 39.12 per cent) displayed, in addition, the following changes (table 2): fibroindurative tuberculosis of one or both apices and occasionally of the subapical regions, minimal apical scarring, fibrocaceous pneumonic tuberculosis, calcified

² Rabin, C. B. Diagnostic Roentgenology, in Nelson Loose Leaf Living Medicine, New York, Thomas Nelson & Sons, 1936, vol 1, pp 91-93

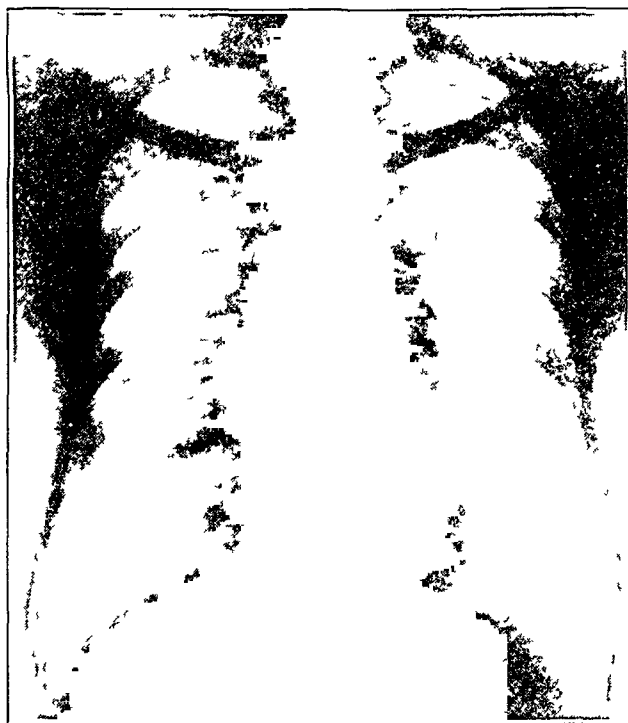


Fig 2—Roentgenogram of the chest of a man aged 43 who had been addicted to the use of heroin (diacetylmorphine) for twenty years



Fig 3—Roentgenogram of the chest of a man aged 30 who had been addicted to the use of heroin (diacetylmorphine) for three years

tuberculosis of one or both upper lobes, bronchiectasis, calcareous pleuritis, interlobar effusion (1 case) and emphysema bullosum (1 case)

In a few cases roentgen examination was done during the height of symptoms caused by withdrawal of the drug. It is interesting to note that in these there was marked accentuation of the thoracic findings and that the serial roentgenograms invariably showed some regression after the symptoms subsided (fig 4)

The cardiac shadow was invariably small and the cardiothoracic ratio³ altered except in cases in which hypertensive or other heart dis-

TABLE 2—*Summary of Roentgen Findings*

Condition	Number of Cases	Per centage
Normal	92	13.50
Changes due to hypertrophic emphysema	207	30.70
Emphysema without increased markings	94	13.94
Increased markings without emphysema	32	4.74
Emphysema with obliteration of the right costophrenic sinus	42	6.23
Emphysema with obliteration of the left costophrenic sinus	19	2.81
Emphysema with obliteration of both costophrenic sinuses	36	5.34
Emphysema and thickening of the right interlobar fissure	66	9.75
Emphysema, increased markings and scarring of the apices	20	2.96
Emphysema, increased markings and bronchiectasis	6	0.89
Fibroindurative tuberculosis without other abnormal features	5	0.74
Fibroindurative tuberculosis with increased markings	39	5.78
Caseous pneumonic tuberculosis bilateral	3	0.44
Calcified tuberculosis of both upper lobes	7	0.04
Calcareous pleuritis, emphysema and increased marking	3	0.44
Calcareous pleuritis without other changes	1	0.14
Emphysema bullosum with increased markings	1	0.14
Right interlobar effusion	1	0.14
Total	674	100

case was present as a complication. Occasionally the pulmonic conus appeared accentuated.

As these structural changes are commonly encountered among non-addicts and as the coexistence of more than one pathologic process may produce similar changes in the lungs, the following questions naturally arose. First, it is likely that the abnormal pulmonary changes had existed prior to addiction, or that they proved to be merely natural sequelae such as are commonly observed in long-standing infections of the upper respiratory tract? Secondly, is it likely that the pathologic

³ Danzer, S. Cardiothoracic Ratio, *Am J M Sc* **157** 513-521 (April) 1919

changes were present because of the coexistence of other diseases, namely, alleigic diatheses, heart disease, asthma, tuberculosis or bronchiectasis? Thirdly, why were the changes more pronounced in cases in which roentgen examination was done during the period of withdrawal? Was this the result of somatic changes⁴ due to deprivation of the drug? Finally, did opium and its derivatives, as well as the other drugs employed, actually produce or enhance the condition? If so, what is the mechanism underlying such an action?

In order to answer these questions it was necessary to examine patients clinically for the purpose of ruling out infectious foci, such as diseased tonsils, carious teeth, infected sinuses and other possible

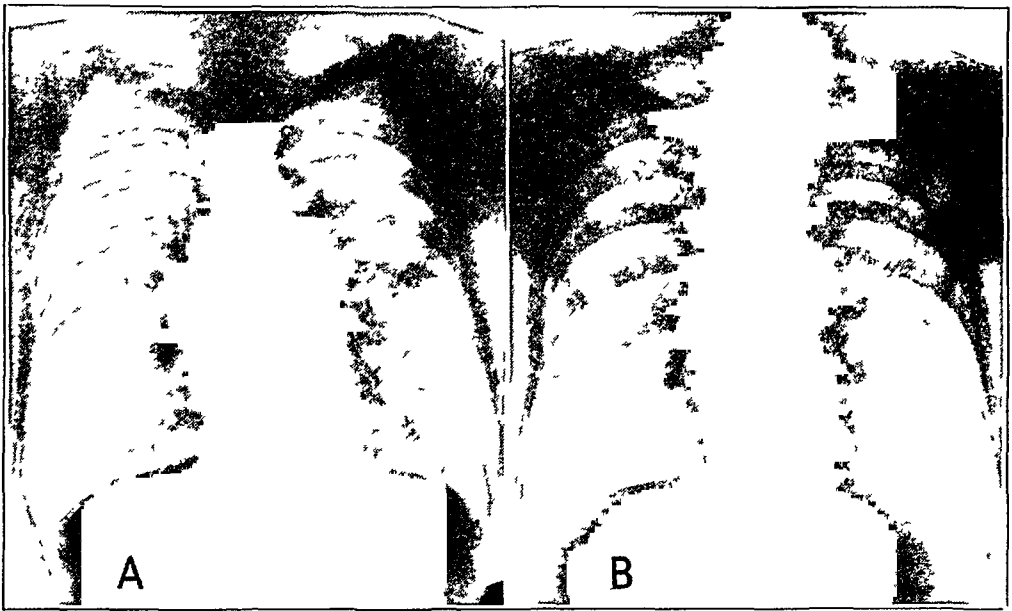


Fig 4—Roentgenograms of the chest of a man aged 41 who had been addicted to the use of heroin (diacetylmorphine) for twenty-two years *A*, film taken at the height of the symptoms which followed withdrawal of the drug, *B*, film taken after these symptoms had subsided

coexistent conditions, since, according to Mullin⁵ and others, these processes may produce identical changes in one of two ways by lymphatic extension through the right side of the heart into the lungs, or by direct extension from the pharynx to the larynx, trachea and bronchi, thus producing emphysema and bronchiectasis Again, Light

4 Wuth, O Zur pathologischen Physiologie der Morphinum-Entziehung, *Klin Wchnschr* **10** 1723 (Sept 12) 1931

5 Mullin, W V Relation of Paranasal Sinus Infection to Disease of the Lower Respiratory Tract, *J A M A* **87** 739 (Sept 4) 1926

and Torrance⁶ have shown in their classic work among addicts the following facts 1 The addicts were all excessive smokers 2 Their hygiene was poor 3 They possessed slovenly habits 4 A good many of them had chronic focal infections

Two distinct groups, therefore, were investigated one of patients without any complaints and apparently in good health, the other of patients with complaints and clinical signs sufficient to warrant hospitalization

ANALYSIS OF ONE HUNDRED CASES

One hundred cases were analyzed in this group Routine physical examinations were performed The average addict was pathetic and somewhat emaciated, without marked external manifestations of specific illness The frontal sinuses and antrums were examined by means of transillumination In 50 cases roentgen examination of all the sinuses was done The remainder of the features of the upper

TABLE 3—*Summary of Findings in One Hundred Cases*

Groups	Number of Cases
Deviated septums	37
Dental caries	29
Diseased sinuses	23
Enlarged and diseased tonsils	16
Chronic pharyngitis	9
Gingivitis	7
More than one focus of infection	30
More than two foci of infection	21
More than three foci of infection	16

respiratory tract were elicited by inspection and auscultation The following observations were made The outstanding abnormality was deviation of the septums (37 cases) Dental caries was next in order (29 cases) This was followed by abnormal sinuses (23 cases), enlarged and diseased tonsils (16 cases), chronic pharyngitis (9 cases) and gingivitis (7 cases) In 63 cases there were no obvious foci In 16, in addition to deviated septums, involvement of the teeth, tonsils, sinuses and bronchi was present

Examination of the chest invariably disclosed signs of emphysema, namely, enlargement of both diameters, hyperresonance, occasionally

6 Light, A B, and Torrance, E G Opium Addiction III Circulation and Respiration of Human Addicts During Administration of Morphine, Arch Int Med **43** 556 (April) 1929 Karr, W G, Light, A B, and Torrance, E G IV Blood of Human Addict During Administration of Morphine, *ibid* **43** 684 (May) 1929

limitation of motion of one or both diaphragms, some diminution of breath sounds and heart sounds, rhonchi, sibilant and sonorous rales and in some cases diffuse wheezing throughout both lung fields. In a few instances there were moist rales at the bases of the lungs.

From table 3 it is obvious that the number of cases in which there were possible foci of infection was not more than 37 per cent. It was probably much smaller, for one is not inclined to regard deviation of the septums without other evidence of infectious foci as a competent cause of structural changes in the lungs. One must therefore consider those patients with more than one focus of infection. This group, according to table 3, constituted 30 per cent. When one compares this number with the total number of patients with abnormal thoracic findings, which was 86.5 per cent, one readily sees that the existent foci of infection could not possibly have produced the changes described in so large a number of persons.

The second group consisted of 80 patients who were confined to the hospital for treatment of acute illnesses. This number was treated at various intervals for forty different diseases. Outstanding among these were acute bronchitis, malaria, syphilis, tuberculosis, malnutrition, bronchial asthma, arteriosclerotic heart disease, duodenal ulcer, psychoses and psychopathic personality. The remaining conditions for which the patients in this group were hospitalized are listed in table 4.

A number of patients had more than one disease during their hospitalization, also, some of the same group were readmitted either because of their original complaints or for some other illness which developed during the period of incarceration.

It is interesting to study the more prevalent diseases for which the addicts were treated. For example, table 4 shows a rather small number of diseases referable to the lungs and upper respiratory tract. Syphilitic patients were few. This may be due to the fact that a good many addicts are homosexual. The incidence of malaria is high. This is a well recognized complication, as has been shown by Biggam and by Boyd and Schlachman⁷ and others. Only 10 patients with pulmonary tuberculosis were admitted to the hospital. The process was active and the sputum yielded tubercle bacilli in less than half of this number. This is certainly a small percentage and not in harmony with the general conception of the prevalence of tuberculosis among drug addicts who are prison inmates. The incidence of duodenal ulcer was also high and warrants further investigation.

⁷ Boyd, L. J., and Schlachman, M. Malaria in Drug Addicts, New York State J. Med. 38: 974 (July 1) 1938.

It has been mentioned that the pulmonary changes were more pronounced in addicts examined by means of the roentgen rays during the height of the withdrawal symptoms. This may be due to a decidedly lowered bodily resistance and possibly to an exacerbation of a chronic infection of the upper respiratory tract, or it may be explained on the basis of somatic changes due to deprivation of the drug. It must be remembered that other unexplained features commonly make their appearance at this stage of the withdrawal period, namely, leukocytosis, glycosuria and albuminuria.

TABLE 4—*Summary of Acute Diseases in Drug Addicts*

Disease	Number of Cases
Acute bronchitis	15
Syphilis	15
Malaria	15
Pulmonary tuberculosis	10
Duodenal ulcer	8
Malnutrition	7
Arteriosclerotic heart disease	4
Bronchial asthma	4
Psychosis and psychopathic personality	4
Pulmonary emphysema with right heart failure	2
Bronchopneumonia	2
Inguinal hernia	2

In addition, 1 case each of the following diseases was observed: Varicosities with ulcers of the lower extremities, acute tonsillitis, cellulitis of the left arm, chronic interstitial nephritis, gastric neurosis, hyperthyroidism, syphilitic heart disease, cerebral edema, acute encephalitis, acute laryngitis, chronic osteomyelitis of the foot, acute catarrhal jaundice, manic depressive psychosis, acute appendicitis, cerebral arteriosclerosis, acute gastritis, intercostal neuralgia, acute cholecystitis, atrophic cirrhosis of liver, mucous colitis, epigastric hernia, foreign body (needle), hepatosplenomegaly, alcoholism, phimosis, pyorrhea alveolaris, hemorrhoids and regional ileitis.

ACTION OF MORPHINE

The question whether opium and its derivatives play an important part in the production of structural pulmonary changes in drug addicts will be answered after a review of some of the literature on the action of morphine and experimental work with this drug on lower animals. Morphine was chosen because it is the most representative drug of the opiate series and also because it was commonly used by the addicts.

According to the literature,⁸ the action of morphine on respiration is selective. In the nonaddict an increased dose of the drug retards

8 Cushny, A. R. *A Textbook of Pharmacology and Therapeutics*, ed. 8, Philadelphia, Lea & Febiger, 1924, pp. 245-258.

respiration and increases its amplitude. The latter action is due to the accumulation of carbon dioxide, which stimulates the respiratory center. In drug addicts, unless very large doses of morphine are taken, there is no appreciable variation in the respiratory rate.⁹ Minor variations in the respiratory rate, therefore, could not have produced the abnormal pulmonary changes.

A more consequential action of morphine is its effect on smooth bronchial musculature. By direct action, it causes first dilatation and later constriction of the smaller bronchi.⁹ The latter is due to an increase in tone of the muscle. (Some pharmacologists believe this to be a peripheral nerve action.) Although this is essentially a laboratory phenomenon, it is not an uncommon clinical experience for a physician to administer "God's own medicine" to a patient with bronchial asthma or status asthmaticus only to pronounce the patient dead soon after the injection. The inference one might draw is that morphine when used excessively over a long period causes bronchial spasm, which in turn may produce pathologic pulmonary changes. I believe that the bronchial spasm which may exist clinically can act only as a contributory factor. This opinion is based on my own observations as well as on the fact that few of the addicts were treated for bronchial asthma. Again, while it is true that morphine and the phenanthrene alkaloids produce contraction of smooth muscle in lower animals, repeated injections of the same drugs fail to bring about similar changes¹⁰ in the same animals.

SUMMARY OF EXPERIMENTAL WORK FORMING THE BASIS OF THESE OBSERVATIONS

Brunelli,¹¹ in his work on cats, was able to demonstrate that morphine sulfate, when injected in amounts of 10 to 20 mg per kilogram of body weight into large decerebrated cats under artificial respiration produced a conspicuous fall in blood pressure in the systemic circulation, a fall in pressure in the left auricle, a temporary rise in pressure in the pulmonary artery and an increase in volume of both liver and lungs. When smaller doses of morphine sulfate were injected he obtained some peripheral and splanchnic vasodilatation and a slight increase in pressure in the pulmonary artery. When 20 mg of morphine sulfate per kilogram of body weight was administered intravenously, an increase in resistance in the lesser circulation and in the liver was noticed. This result, according to Brunelli, was due to a change in the

9 Jackson, C, Jr, in Cushny,⁸ p 257

10 Cushny,⁸ p 253

11 Brunelli, B. L'influenza della morfina sul regime tensivo del grande e del piccolo circolo, Arch di farmacol sper 57 78 (Feb 1) 1934

capillary permeability with the tendency to absorb water. At the same time there was a change in the osmotic pressure of the pulmonary colloids, with absorption of water in the pulmonary veins. Two factors, therefore, were present: (1) with higher doses of morphine sulfate used intravenously, an increase in the capillary permeability and a tendency of the pulmonary colloids to absorb water, (2) a decrease of the osmotic pressure of the blood. Both phenomena produced a shift of a considerable volume of water from the blood into the tissues.

If Brunelli's laboratory findings are correlated with my clinical observations it becomes understandable why so large a number of addicts displayed increased bronchovascular markings and emphysema of the lungs. Incidentally, Brunelli's work may also explain the frequent appearance of obliteration of the costophrenic sinuses and thickening of the right interlobar fissures in so many (175, or 24.3 per cent) of my cases (table 2). These changes may represent organization of fluid in the free pleural space and in the interlobar fissure which is probably the result of transudation due to altered capillary permeability.

Luisida,¹² working independently of Brunelli, was able to show similar findings. He assumed that morphine sulfate, because of its action on smooth bronchial musculature and the resultant increase in tone, may exert a similar action on the pulmonary veins and thus influence the pulmonary circulation.

By means of oncometric readings, Luisida succeeded in demonstrating, among other changes, the following phenomena. After administration of morphine sulfate in large doses into the veins of cats, a rise of pressure in the pulmonary veins, an increase of pressure in the pulmonary artery and an increase in volume of the lungs were noticed. It was also observed that after the injection of the drug after a considerable period there was a fall in pressure in the pulmonary arteries, originating in the heart and not in the blood vessels. Luisida concluded that in addition to the direct action of the drug on smooth muscle the pulmonary veins are possessed of an important narrowing apparatus which is sensitive to morphine sulfate.

COMMENT

The problems which are discussed are as follows: the existence of abnormal pulmonary roentgen findings in 86.5 per cent of drug addicts, about 30 per cent of whom showed foci of infection of the upper

¹² Luisida, A. Neue Untersuchungen über die Wirkung des Morphiums auf Blutgefäße, besonders Lungengefäße, *Arch f exper Path u Pharmakol* **132** 296, 1928.

respiratory tract on routine physical examination, the evaluation of individual factors, such as chronic infections of the upper respiratory tract and diseases not necessarily related to the lungs, and the possible modes of production of the changes described. An attempt is made to establish physiologic principles on which the observations might be based.

I agree with other workers that infections of the upper respiratory tract play an important role in the production of structural changes in the lungs. However, in the present group of cases the maximum number in which there were obvious foci of infection was only 30 per cent. This leaves 70 per cent of cases in which there were abnormal pulmonary findings unexplained by any apparent etiologic factor. Again, it must be conceded that not all persons with foci of infection have diseases of the lungs. The age range itself (average 39 years) tends to rule out such marked pulmonary changes among so many persons. Of the diseases which coexisted or developed during the period of incarceration, only tuberculosis is to be considered. Tuberculosis in all its forms constituted only 7 per cent (table 2).

In the discussion of modes of production of structural changes in the lungs the experimentally produced effects of morphine on smooth muscle are considered. This, as has been mentioned, is not without clinical significance. Finally, the experimental work of Brunelli and Luisida lends strong support to the conception that morphine sulfate when used in large doses over a prolonged period will produce definite structural pulmonary changes as well as alteration in the pulmonary circulation.

SUMMARY AND CONCLUSIONS

Roentgen examination of the chests of several thousand drug addicts at the Riker's Island Hospital has been made in the past five years, a preponderant number displayed abnormal findings.

During the past fifteen months 674 addicts were studied by means of thoracic roentgenograms.

Over 85 per cent presented abnormal pulmonary findings. The commonest changes observed were those characteristic of hypertrophic emphysema (30.7 per cent). The remainder showed varied pathologic features, *i. e.*, atrophic emphysema (13.94 per cent), increased bronchovascular markings (70.16 per cent), emphysema associated with obliteration of costophrenic sinuses and thickening of the right interlobar fissure (24.13 per cent) and fibroindurative tuberculosis (5.78 per cent).

One hundred patients were examined for infections of the upper respiratory tract. The maximum number of cases in which such foci

could possibly have played a contributory role in the production of the pulmonary abnormalities was 30 per cent

Eighty addicts were confined in the hospital for a number of different diseases which did not have any bearing on the changes described

The abnormal pulmonary features were somewhat more pronounced in patients on whom roentgen examination was done during the height of the period of withdrawal. This was probably due to somatic changes

A summary of the experimental work of Brunelli and Luisida shows conclusively that a definite relation exists between the use of morphine sulfate and pulmonary pathologic changes in lower animals

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

JOSEPH EARLE MOORE, M D

AND

CHARLES F MOHR, M D

BALTIMORE

The material for this article has been selected from publications which appeared from July 1938 to June 1939. As in previous reviews,¹ it has been necessary to select material rigidly. Little attention has been paid to serologic aspects of the subject, and case reports have been almost wholly eliminated.

HISTORY OF SYPHILIS

In a charmingly written article, Zimmermann² describes epidemics of extragenital syphilis occurring between 1497 and 1624. Most of these epidemics had their origin from cupping in public baths. An outbreak of syphilis occurred in Frankfort on the Main, Germany, in 1496. The city authorities, after consulting with the three city physicians, ordered the keeper of the Red Bath to discharge his "poxed" helper or the bath would be closed. A later epidemic, in Brunn, Czechoslovakia, is described in a treatise by Thomas Jordanus, which was published in 1580. Zimmermann offers his own translation of this treatise. Jordanus describes the suffering of those afflicted as follows:

Here [the bath outside the Green Gate] the scourge had its origin, here its seeds were conceived. For on that day of winter which astronomers determine by the entrance of the Sun into the Ram, commonly called the feast of St. Lucia [December 13], a fortnight before the Christmas holidays, in the coldest part of the winter of 1577, whosoever entered the stew on this day and had their skin scarified and were cupped, all were said to have been infected. They experienced

Reprints of this article are not available.

From the Syphilis Division of the Medical Clinic, Johns Hopkins University and Hospital.

1 (a) Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch Int Med* **56** 1015 (Nov) 1935. (b) Padget, P., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid* **58** 901 (Nov) 1936, (c) **60** 887 (Nov) 1937. (d) Padget, P., Sullivan, M., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid* **62** 1029 (Dec) 1938.

2 Zimmermann, E. L. Extragenital Syphilis as Described in the Early Literature (1497-1624), with Special Reference to Focal Epidemics, *Am J Syph, Gonorr & Ven Dis* **22** 757 (Nov) 1938, **23** 104 (Jan) 1939.

no harm at once. The symptoms of the disease did not appear immediately. In some, they remained latent for eight days. In others, they remained hidden for two weeks, even for a month, according (as the saying goes) to the strength of the infecting agent or the resistance of the patient. Meanwhile they were oppressed by a strange torpor. They were listless in performing their usual duties and depressed. Neither mind nor hand and foot functioned. They were seen wandering about aimlessly, more like shadows than men. The natural color of their faces had paled, the luster of their eyes had dimmed and dark circles had developed like those seen in menstruating women. Then frank symptoms of the disease manifested themselves. The cupped areas swelled and were invaded by an intense and intractable heat, followed by abscesses and foul ulcers, flowing with sanies and corruption. Scattered about to the extent of the palm of the hand were pustules. The areas were studded with small abscesses, which, upon being opened either with a knife or with topical applications, discharged a thin, serous, foul phlegm. In others, the discharge was corrosive. The flesh surrounding the site of cupping became foul and corroded and gave forth a stench as comes from Telephian and phagedenic ulcers. To begin with, it was astonishing that from so many cups applied (some had about ten, several about three times that number, applied), of all these, only one, or at most two, developed into foul ulcers, with the lone exception of the mother-in-law of Lawrence, the tailor, who had three ulcers develop out of fifteen cups applied. In many the entire body was covered with pustules, the countenance was horrid to look at. The back, chest, abdomen, feet, indeed the entire body from head to toes, were defiled by a scabby itch, with crusted ulcers but slightly raised above the level of the skin, the size of a two kreutzer piece or of a thumb nail, with a red halo and a glistening surface as in the condition called by barbarous authors [Arabians and Arabists] *tinea*. From these oozes a thick, sluggish mucus. When the scabs drop off and the lesions heal, there are left behind dark spots, of a leaden or brownish color, differing from freckles or vitiligo. As the disease progressed, hard tumors (calli) formed on the scalp, which, upon being ruptured or cut open to the great pain and amid the loud cries of the patient, discharged a honey-like, resinous substance. Following closure of these foul and malignant ulcers, so difficult to cleanse and no less difficult to fill in with new flesh, further symptoms erupted. All the joints of the body, the forearms, the shoulders, the elbows, the arms, the calves, the shins, the feet, were excruciatingly racked with stabbing pains, as if pierced by sharp instruments, as if they were being gashed with knives or burned with hot forceps. Most intense is the pain where the tibia is bare of flesh, uncovered by the bellies of muscles and invested only by periosteum. Their heavy limbs required support. They cannot be sustained or raised through their own strength. Some, indeed, when their paralysis has abated somewhat, must be lifted upon the shoulders of others. There is no rest. There is constant shouting and weeping, groaning over pains which never cease, especially at night when the weary limbs are ordinarily restored by peaceful sleep. They lie awake throughout the night. At dawn a false shadow of peace falls upon them. But their torments recur. If they accuse the day of being hostile and spiteful, they must indeed abhor the image and recollection of night. These nights of anguish were not numbered by one or a few, but lasted a whole month. In vain they crammed themselves with remedies.

The second half of Zimmermann's paper deals with outbreaks of extragenital syphilis as a result of wetnursing and midwifery during the latter half of the sixteenth century. He provides translated paragraphs from treatises by Ambroise Paré, Antonius Brassavolus and the midwife Louise Bourgeois.

Goodman³ gives some fifty references to the early literature (1500-1900) dealing with syphilis in childhood

A Pueblo skull, identified as Tuzigoot II-50, found during the excavation of the Tuzigoot ruins near Clarksdale, Ariz, is described by Denninger⁴ Tuzigoot was occupied probably before 1000 A D and abandoned shortly after 1350 A D The lesions found in the skull are thought to be typical of syphilitic lesions of bone

SPIROCHAETA PALLIDA

Staining—Haie⁵ describes a new method for staining *Spirochaeta pallida* Aqueous stains, because of their high surface tension, penetrate poorly Alcohol, although of low surface tension, penetrates poorly because it coagulates tissue The author therefore suggests using hexylresorcinol as a solvent for the dye In the technic described, a 1 per cent solution of gentian violet in hexylresorcinol is employed The method as described by the author is simple, but in our hands it has not proved entirely satisfactory

Garvin⁶ and Ono⁷ also suggest new staining methods, and Krajian,⁸ whose method was first discussed in these reviews in 1936, presents an additional description of it The clinical application of Krajian's staining technic in a large hospital laboratory is discussed in two papers by Chambers and Scholtz, to be referred to presently

Culture—Renewed failure in attempts to culture virulent *S pallida* are reported by Bessemans and de Meersman⁹ and by Crespel, Delavenne and Huberty¹⁰ The biologic nature of those strains of spirochetes which can be cultured successfully (all avirulent) is discussed by Koch¹¹

3 Goodman, H Historic Pronouncements on Syphilis in Children, Arch Pediat **55**.651 (Oct) 1938

4 Denninger, H S Syphilis of Pueblo Skull Before 1350, Arch Path **26** 724 (Sept) 1938

5 Haie, R D A Practical Method of Staining Treponema Pallida by Means of Low Surface Tension Stain, J Lab & Clin Med **23** 1215 (Aug) 1938

6 Garvin, T Spirochetal Stain on Paraffin Section, Am J Clin Path, Tech Supp **2** 144 (July) 1938

7 Ono, K Färbung der Spirochäten im Strichpräparate mittels Kal Permanganatlösung, Acta dermat **31** 69, 1938

8 Krajian, A A A Reliable Method of Staining Spirochaeta Pallida in Smears, Arch Dermat & Syph **38** 427 (Sept) 1938

9 Bessemans, A, and de Meersman, E Tentatives de culture de Tréponemia pallidum sur la membrane chorio-allantoïdienne de l'embryon de poulet vivant, Compt rend Soc de biol **127** 847, 1938

10 Crespel, C, Delavenne, E, and Huberty, V Sur quelques souches de culture du tréponème de Schaudinn, Arch Inst prophylac **10** 89, 1938

11 Koch Zur Biologie der Pallidakultur, Arch f Dermat u Syph **177**.216, 1938

Dissemination—Levaditi, Vaisman and Rousset-Chabaud¹² grafted bits of rabbit testicular syphiloma on the backs of mice, which were killed at intervals of from two to forty-two days. When the inoculated areas were studied histologically, it was found that spirochetes had entered the neighboring lymphatics by the second day, by the forty-second day there was a generalized infection of the lymphatic system. Spirochetes were also present in the walls of the blood vessels¹⁸ in the infected region on the first, third and fifth day after infection, and blood from infected mice was infectious for rabbits on the first, third, twelfth and thirty-fifth days.

PINTA CAUSED BY ORGANISM MORPHOLOGICALLY IDENTICAL
WITH *S. PALLIDA*

Pinta, a cutaneous disease practically limited to tropical America, has been previously thought to be due to fungus infection. It is an extremely chronic disease, which may attack the skin of the entire body (but not the viscera or nervous system so far as is known) and which shows no tendency to spontaneous cure. A group of workers in Habana, Cuba, headed by Sáenz, has discovered an organism which is morphologically identical with *S. pallida* (both in dark field and stained preparations) in serum obtained from skin scrapings and lymph nodes. These observers have demonstrated the newly discovered spirochete in 94 per cent of 127 patients examined in Cuba and Mexico, their findings are said¹³ to have been confirmed by Pardo-Castello. Moreover, some evidence has been found which suggests that the disease is transmitted by an insect vector (*Simulium haematopotum*). The details of these new studies are supplied in papers by Leon y Blanco,¹⁴ by Saenz, Grau Triana and Alfonso Armenteros,¹⁵ by Curbelo and Conde Mateo¹⁶ and by Gonzales Herrejón and Ortiz Lombardini.¹⁷

12 Levaditi, C, Vaisman, A, and Rousset-Chabaud, D. Le mecanisme de la dispersion treponemique chez les souris atteintes de syphilis expérimentale cliniquement inapparente, *Bull Acad de med, Paris* **119** 154 (Feb 1) 1938.

13 Discovery of the Causative Organism of Pinta, editorial, *Arch Dermat & Syph* **39** 709 (April) 1939.

14 Leon y Blanco, F. Sobre un Treponema encontrado en los enfermos de "mal del pinto," *Medicina, México* **18** 617 (Dec 25) 1938, *Estudios sobre la etiología del "mal de pinto,"* *ibid* **18** 624 (Dec 25) 1938.

15 Saenz, B, and Grau Triana, J. Estado actual del problema de la pinta en Cuba, *Rev de med y cir Habana* **44** 1 (Jan 31) 1939. Saenz, B, Grau Triana, J, and Alfonso Armenteros, J. Reseña historica del "mal del pinto" en nuestro pais, *Rev med cubana* [**50**] 21 (Jan) 1939.

16 Curbelo, A, and Conde Mateo, E. Ensayos experimentales sobre el agente causal de la pinta encontrado en Cuba, *Rev med cubana* [**50**] 25 (Jan) 1939. Curbelo, A, Castro Palomano, J, Conde Mateo, E, and Gaizon, L. Ensayos experimentales sobre el agente causal de la pinta encontrado en Cuba, *Rev de cien med* **1** 134 (Oct) 1938.

EXPERIMENTAL SYPHILIS

Congenital Syphilis—Kemp and Fitzgerald¹⁹ and Takahashi²⁰ add further experimental evidence to show that congenital syphilis does not occur in mice and rabbits. Indeed, Kemp and Fitzgerald observed no effect on the growth and development of the litters of infected mothers, though Takahashi found a high incidence of abortion and of various dystrophies among the animals which survived. Kemp and Fitzgerald add the further important contribution that there was no evidence of immunity transmitted from infected mothers to healthy offspring, since the latter could be as readily infected with syphilis as could young rabbits from normal mothers.

Aortic Syphilis in Rabbits—Takahashi²¹ studied the histopathologic changes of the aortic wall in 168 syphilitic and 50 nonsyphilitic rabbits (among the latter 13 with yaws, 3 with rat bite fever and 34 that were normal). Twenty-nine (17.2 per cent) of the syphilitic animals, and none of the nonsyphilitic group, were found to have lesions in the aorta. Twelve of the syphilitic animals had small saccular aneurysms. The histopathologic picture in 25 aortas was similar to that found in so-called epinephrine sclerosis or in spontaneous arteriosclerosis, in 4 it resembled that seen in syphilitic mesaortitis in man. In 2 instances *S. pallida* was demonstrated in the aortic wall by successful subcutaneous inoculation of normal rabbits, though unfortunately Takahashi does not record the number of unsuccessful attempts.

Syphilis and Yaws—As a contribution to the argument over the identity of syphilis and yaws, Ferris and Turner²² inoculated animals with three strains each of *Spirochaeta pertenuis* and *S. pallida* and

17 Gonzales Herrejon, S. Resumen histórico de las principales ideas etiologicas respecto al "mal del pinto," *Medicina, México* **18** 619 (Dec 25) 1938. Gonzales Herrejon, S., and Ortiz Lombardini, M. del C. ¿Es el *Simulium haematopotum* (Malloch) transmisor del mal del pinto? *ibid* **18** 631 (Dec 25) 1938.

18 Levaditi, C. Vaisman, A., and Rousset-Chabaud, D. (Mme.) Mode de dispersion du virus syphilitique dans l'organisme de la souris atteinte de syphilis experimentale cliniquement inapparente. Rôle de la circulation sanguine, *Bull Acad de med, Paris* **120** 191 (Oct 11) 1938.

19 Kemp, J. E., and Fitzgerald, E. M. Studies in Experimental Congenital Syphilis and the Transference of Immunity from Immune Syphilitic Female Rabbits to Their Offspring, *J Invest Dermat* **1** 353 (Oct) 1938.

20 Takahashi, H. Experimentelle Untersuchungen über die angeborene Syphilis, *Jap J Exper Med* **16** 1 (Feb 20) 1938.

21 Takahashi, H. Beiträge zur histopathologischen Untersuchung der experimentellen Syphilis und Frambosie bei Kaninchen. Pathologische Veränderungen der Aortenwand, *Jap J Exper Med* **15** 321 (Oct 20) 1937.

22 Ferris, H. W., and Turner, T. B. Comparison of Cutaneous Lesions Produced in Rabbits by Intracutaneous Inoculation of Spirochetes from Yaws and Syphilis, *Arch Path* **26** 491 (Aug) 1938.

subsequently studied the gross and microscopic character of the lesions produced. On the whole, and although the cellular reactions were qualitatively identical for lesions of approximately the same size, the lesions of yaws developed more slowly, were smaller, contained fewer spirochetes and involuted more rapidly than the lesions of syphilis.

Syphilis and Cirrhosis of the Liver—When Ferris²³ produced cirrhosis of the liver in syphilitic and control rabbits by chronic chloroform poisoning, the extent of the cirrhosis was approximately the same in both groups, suggesting that in this animal, at least, syphilis plays no part in the production of cirrhosis.

Effect of Antisyphilitic Drugs on the Sexual Cycle—Ogihara²⁴ observed that when female rats were given bismuth preparations ovulation stopped. Aisphenamine and mercury preparations had no such effect. However, the combination of aisphenamine and a bismuth compound had the same effect as the bismuth compound alone.

Syphilis in Lower Monkeys—There has been some disagreement as to whether lower monkeys could be infected with syphilis. Bessemans, de Wilde and van Thielen²⁵ have been able to infect 2 of 6 monkeys (*Macacus rhesus*), using massive inoculums, by scarification of the eyebrow or by scrotal or testicular injection. In none of the animals did clinical evidence of syphilis develop but 1 monkey later had a positive serologic test for syphilis, and in the case of this animal and 1 other it was possible to prove infection by lymph node transfer of the disease to normal rabbits.

Chemotherapy and Fever—Borchers²⁶ studied experimentally the therapeutic effect of combined fever and chemotherapy. His experiment was carried out on three groups of rabbits. 1. Three syphilitic rabbits were given fever (maximum, 41.7 C [106 F]) by the administration of a vaccine (Stimulol, a mixed vaccine) without other treatment. The syphilitic lesions increased in size. 2. Three control animals were given three doses (7 to 8 mg. per kilogram) of neoaisphenamine at forty-eight hour intervals. The lesions healed, but two relapsed, one in thirty-six days, the other in thirty-two days. The third animal died before

23 Ferris, H. W. Cirrhosis of the Liver in Rabbits with Continued Chloroform Poisoning and with Associated Syphilitic Infection, *Arch. Path.* **26** 1023 (Nov.) 1938.

24 Ogihara, M. Experimentelle Studien über den Einfluss der antiluetischen Präparate auf den Sexualzyklus, *Mitt. a. d. med. Akad. zu Kyoto* **23** 713, 1938.

25 Bessemans, A., de Wilde, H., and van Thielen, E. Syphilis inapparente du macaque et résistance à la pallidoïdose, *Compt. rend. Soc. de biol.* **129** 373, 1938.

26 Borchers, G. Tierexperimentelle Beiträge zur Fiebertherapie des Syphilis, *Arch. f. Dermat. u. Syph.* **176** 705 (June) 1938.

completion of the experiment. 3 In the third group fever and neoarsphenamine were combined, three doses (8 mg per kilogram) of neoarsphenamine being given at a time when the body temperature was 41 to 41.7 C (105.8 to 106 F). The lesions disappeared promptly in all, and there was one instance of relapse among 4 animals.

While the dose of 8 mg per kilogram is distinctly subcurative (curative dose of neoarsphenamine, 15 to 25 mg per kilogram), the author studied the effect of still smaller doses, alone and in combination with fever. When 3 mg per kilogram of neoarsphenamine was given alone to a syphilitic rabbit, there was no effect on lesions or organisms, when this same dose was combined with fever (41 C) in 2 animals, motile organisms disappeared from the testicular syphilomas within twenty-four to forty-eight hours.

This is an interesting experimental confirmation of the clinical suggestion of Simpson and Kendell, referred to in last year's review.¹⁴

Artificial Heat—Beck²⁷ infected mice with *S. pallida* and fifty-eight to four hundred and sixty days after inoculation treated them with artificial fever (produced by hot air). He found that if a rectal temperature of 104 F or more was maintained continuously for thirteen and a half hours, the organisms disappeared from the brain as well as from other tissues in two thirds of the mice. However, if the mice were treated by a series of short fevers, lasting fifteen minutes at a time, spirochetes disappeared in only one fourth of the animals.

For many years those familiar with experimental syphilis in the rabbit have known that in the heat of summer the incubation period of syphilis in that animal is prolonged, local lesions are inconspicuous, and generalized lesions of syphilis are absent. In modern syphilis laboratories, therefore, the animal rooms are air conditioned. Chorazak,²⁸ apparently not aware of this fact, attempts to explain the summer phenomenon of syphilis in rabbits on the basis of dietary change. By varying the vitamin content of the diet he found that when an abundance of vitamin B₁ was fed the incubation period of syphilitic lesions was prolonged. An excess of vitamins A and D appeared to shorten the incubation period. The experiment is interesting in the light of the clinical improvement said to occur occasionally in tabes dorsalis when vitamin B₁ is administered.²⁹

27 Beck, A. The Influence of Artificially Induced Fever upon Syphilitic Infection of Mice, *Brit J Ven Dis* **14** 221 (July) 1938.

28 Chorazak, T. Der Einfluss der Vitamine auf die Entwicklung der syphilitischen Impfveränderungen in der experimentellen Kaninchensyphilis, *Bull internat Acad polon d sc et d lett, Cl méd* **214** 219 (Feb) 1938.

29 Metildi, P. F. The Treatment of Tabetic Lightning Pains with Thiamin Chloride. Preliminary Report, *Am J Syph, Gonorr & Ven Dis* **23** 1 (Jan) 1939.

Effect of Hibernation on Syphilis—Bessemans, de Wilde and de Moor³⁰ have confirmed the work of Jahnelt,³¹ who demonstrated that the rell-mouse (a hibernating animal) if inoculated with *S pallida* prior to hibernation is free of syphilitic infection after the hibernating period. Jahnelt believed that the disappearance of the syphilitic infection was due to an immune humoral response rather than to a lowering of body temperature. Bessemans and collaborators were able to produce syphilitic infection in the hedgehog and hamster and noted that after hibernation lymph node transfers from these animals gave negative results. Node transfers from control animals kept in a warm environment to prevent hibernation gave consistently positive results. Artificial hibernation brought about by placing the hamster and hedgehog in a refrigerator for a period of twenty days resulted in disappearance of the syphilitic infection.

Immunity—In one of the most important papers of the year, Turner³² has clearly demonstrated that immunity in syphilitic rabbits is at least partly humoral. By a series of appropriate experiments he has shown that when an emulsion containing virulent *S pallida* is added to serums from normal rabbits and from untreated immune syphilitic rabbits infected with a homologous strain of *S pallida* and the mixtures after incubation at 37 C are injected intracutaneously into normal rabbits, typical syphilitic lesions commonly develop at the sites of inoculation of the normal serum-spirochete mixture, while at the sites of inoculation of immune serum-spirochete mixtures, usually either no lesions develop or the incubation period of the resulting lesions is shorter and the lesions remain smaller than those produced by normal serum-spirochete mixtures.

In a series of preliminary experiments, of 56 areas inoculated with syphilitic serum-spirochete mixtures, the suppressive action of the syphilitic serum was manifest in 42, in 10 areas questionable evidence of protection was noted, and in 4 areas there was no evidence that the syphilitic serum had exerted a suppressive or protective action.

The results of the protection test in three other series of experiments were as follows: 1. Of 12 areas in 6 rabbits inoculated with normal serum-spirochete mixtures, typical syphilitic lesions developed in all, while in the same number of areas inoculated with immune serum-

30 Bessemans, A., de Wilde, H., and de Moor, A. Effet du sommeil hibernant sur la syphilis du hamster et du hérisson, *Compt rend Soc de biol* **129** 376, 1938.

31 Jahnelt, F. Ueber den Einfluss des Winterschlafes auf die Syphilisspirochäten in Gehirn und den inneren Organen des Siebenschlafers. Ein Beitrag zur Frage der Selbstheilung bei der tierexperimentellen Syphilis, *Arch f Dermat u Syph* **171** 187, 1935.

32 Turner, T. B. Protective Antibodies in the Serum of Syphilitic Rabbits, *J Exper Med* **69** 867 (June) 1939.

spirochete mixtures there was complete or partial suppression of lesions in all 2 Of 45 areas inoculated with spirochetes plus serum from 10 different immune syphilitic rabbits, definite evidence of protection was observed in 37, questionable evidence in 5 and no evidence of protection in 3 3 In 8 areas in 4 rabbits inoculated with immune serum-spirochete mixtures, no lesions developed during the period of observation, while in each of 8 areas in the same rabbits inoculated with one of two normal serum-spirochete mixtures typical syphilitic lesions developed

From these experiments Turner concludes, therefore, that during the course of syphilitic infection in rabbits specific humoral antibodies develop which can be demonstrated by an appropriate "protection test" The presence of these antibodies is associated with a high degree of acquired immunity to the disease

Chesney, as a part of his important work on immunity in syphilis, has studied with Woods and Campbell,³³ the extent to which the eye participates in the general resistance which develops in rabbits during syphilitic infection Forty-three treated immune animals were inoculated with the homologous strain of *S. pallida*, the inoculum being introduced either into the cornea or into the anterior chamber Forty-one normal animals were used as controls Of the immune animals, 27 (62 per cent) showed lesions in the cornea, of the controls, 90 per cent developed corneal lesions The authors continue

The lesions developing in the corneas of the "immune" animals had a longer incubation period on the average, were often of longer duration, and in some instances were more severe than the lesions developing in the control animals In the case of some animals, also, they showed a greater tendency to recur

It is concluded that the eye of the syphilitic rabbit does not share to the same extent as other tissues in the general resistant state which develops in that animal during the course of syphilitic infection

In their discussion of these results, the authors say

The results of these experiments offer a possible explanation for the well established clinical observation that the interstitial keratitis of congenital syphilis is prone to recur in patients with that condition one might infer that this tendency to recur is due to failure of the cornea of the patient with congenital syphilis to participate in the general defense reaction against the infection Such an inference would suffice to explain the tendency of such patients to show repeated relapses of interstitial keratitis, but would not explain the fact that this condition is singularly resistant to antisypilitic treatment Some ophthalmologists, notably Igersheimer and Derby, have sought to explain the proneness of interstitial keratitis to relapse on the basis of allergy The experiments reported in this communication lend no support to this view Furthermore, attempts made by us to

33 Chesney, A. M., Woods, A. C., and Campbell, A. D. Observation on the Relation of the Eye to Immunity in Experimental Syphilis, *J. Exper. Med.* **69** 163 (Jan.) 1939

sensitize the corneas of normal rabbits to *T pallidum* by the preliminary injection of killed suspensions of that organism were entirely fruitless there is no direct evidence that such [allergy] is the case,

SERODIAGNOSIS OF SYPHILIS

As in previous years, it is impossible, because of limitations of space, to refer to the large volume of technical papers dealing with the serodiagnosis of syphilis. Only a few of those which present details of practical importance to the clinician can be mentioned.

In October 1938 there was held an assembly of laboratory directors and serologists under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis and the United States Public Health Service, at which seventeen papers (later published as a symposium³⁴) were presented and certain recommendations adopted. Among the essayists were Parran, Eagle, Hinton, Kahn, Kline, Kolmer, Mahoney and Harrison, Hazen, Seneor, Moore, Perry, Hoyt, Casselman, Sanford, Whittemore, Giordano, Wadsworth and Lamb, the discussants included, among others, Godfrey, Lange, Nelson, Sherwood and Stokes.

The symposium dealt with four topics: (1) the need for adherence to conventional technics in the reliable routine performance of serologic tests for syphilis, (2) improvement of methods for determining the efficiency of the performance of serologic tests, (3) training of laboratory personnel, and (4) the desirability of state departments of health approving or licensing laboratories for the performance of serodiagnostic tests for syphilis. There were also descriptions and demonstrations by Eagle, Hinton, Kahn, Kline and Kolmer of the latest developments in their several technics.

Need for Adherence to Conventional Technics—In the recommendations of the committee on this topic appears the following:

[There is] great variation in the results obtained in various State, hospital and private laboratories. The poorest results were usually obtained when there was considerable divergence from the technic described by the originator of a method. Experience has shown that modifications which involve considerable divergence from the conventional technic described by the originator should not be attempted except as a research project in laboratories adequately equipped with personnel and material for the conduct of such investigations.

Improvement of Methods for Determining the Efficiency of the Performance of Serologic Tests—After the presentation of six pertinent papers on this topic, the committee concluded that a system of checks of serologic performance should be set up in each state, with a laboratory of proved efficiency (state health department or other) setting a standard of specificity and sensitivity in performance against

34 The Serodiagnosis of Syphilis, Ven Dis Inform, 1939, supp 9

which participating laboratories might measure their own results. *To qualify as satisfactory, a laboratory should attain a sensitivity rating not more than 10 per cent below that of the control laboratory and a specificity rating of not less than 99 per cent* (The italics are ours.)

These recommendations should be widely publicized and should be familiar to clinicians as well as to laboratory directors. Even yet there is too little clinical appreciation of the fact that serodiagnostic tests for syphilis are not exactly standardized or standardizable procedures and that, in order to avoid diagnosing syphilis in noninfected persons or missing the disease in those who are infected, the clinician should know not only what technic the laboratory of his choice employs but also how efficient that laboratory is when checked against known good performance.

In order to simplify the interpretation of serologic results by clinicians, the committee also repeated and emphasized the recommendation repeatedly stressed by three League of Nations serologic conferences, beginning in 1923:

"Qualitative serodiagnostic tests should be reported as positive, doubtful, or negative" (the italics are ours), and the confusing system of plus marks so commonly employed should be abandoned.

It was also emphasized by one of the essayists (Moore) that the quantitative serologic test, by whatever method quantitation is carried out, has absolutely no diagnostic value whatever for the practitioner, and as yet it has comparatively little for the expert. At present the value of the quantitative serologic test lies in the research rather than in the practical field.

In the discussion there was general agreement as to the recommendation that tests be reported as positive, doubtful and negative, except from Kolmer, who wished to divide the term "positive" into "strongly positive" and "weakly positive" and who has subsequently defended his stand in a separate paper³⁵. It was pointed out, however, that this adoption of terms was, in effect, a retention of the obsolete system of plus marks and an attempt at rough (wholly valueless) quantitation. If the serologist means by the term "weakly positive" that he thinks the patient probably has syphilis, the word "weakly" is superfluous. If, on the other hand, the serologist is dubious as to the interpretation of a weakly positive result, a better term is "doubtful," a word which deliberately interjects into the clinician's mind the meaning the serologist intends to convey.

The discussion of the value of quantitative tests in diagnosis was especially pertinent because of the adoption by the New York State

³⁵ Kolmer, J. A. Concerning the Method Proposed for Reporting the Serological Reactions for Syphilis as Positive, Doubtful and Negative, *Am J Clin Path* 9 121 (March) 1939.

Department of Health Laboratory of an esoteric quantitative technic for routine diagnostic purposes (Wadsworth, Maltaner and Maltaner,³⁶ Maltaner³⁷) This technic differs from the quantitative technics used in most laboratories at the present time in two respects (1) complement is titrated against a fixed amount of serum rather than serum being titrated against a fixed amount of complement, and (2) the results are reported in terms of units calculated from the following ratio

$$\frac{\text{Amount of complement required for 50 per cent hemolysis with serum and antigen}}{\text{Amount of complement required for 50 per cent hemolysis with serum alone}}$$

Discussion of the complex technical details of the quantitation of the Maltaner technic, of the value of this procedure as compared with direct quantitation of serum reagin or of the probable error introduced by the varying anticomplementary activity of different serums is here purposely avoided. Not only is the test itself complicated and unsuited for general performance, but the manner of reporting the results to the clinician is equally complicated and subject to gross misinterpretation, as may be seen from the following paragraph which appears on the reverse of the New York State serologic report blank

The quantitative complement fixation test for syphilis permits reporting a numerical value which is a direct index of the degree, or titer, of the reaction. When no reaction occurs, i. e., when the fixation is the same in the test and control, the numerical value of the titer is 1, when the fixation is twice as great in the test as in the control, the titer is 2, etc. A titer of 15 has been observed with an extremely small percentage of specimens from healthy individuals. Titers of less than 15 have been recorded in the known cases of syphilis when intensively treated, although in some such cases titers of 2 or more may occur occasionally. Whether or not titers slightly in excess of 2 occur in conditions other than syphilis is not known, and therefore the significance of reactions of this degree should be carefully considered. *As a rule, the higher the titer the greater its significance in diagnosis* [The italics are ours. The italicized statement has no present basis in fact.] Specimens with titers greater than 6 have given reactions of complete fixation (4+) with the previous method. Titers of 100 or greater have been determined in a few cases under special investigation, but it is not practicable at the present time to report the degree of reactions when the titers are greater than 10.

Training of Personnel and Licensing of Laboratories—The papers dealing with these points and the discussion at the assembly of laboratory directors are of greater public health than of general medical interest and will be omitted here.

36 Wadsworth, A., Maltaner, F., and Maltaner, E. Quantitative Studies of the Complement-Fixation Reaction with Syphilitic Serum and Tissue Extract. Technic of the Practical Quantitative Test, *J. Immunol.* **35** 217 (Sept.) 1938.

37 Maltaner, E. Serologic Tests in the Diagnosis of Syphilis, *Am. J. Pub. Health* **29** 104 (Feb.) 1939.

"Presumptive," "Exclusion" and "Screen" Tests—An editorial commentator in *The Journal of the American Medical Association* writes as follows ³⁸

An increasing widespread use is apparent of tests for syphilis said to be so sensitive that a negative result "excludes" syphilitic infection while a positive result is "presumptive" evidence of syphilis. Confirmation by a less sensitive and more specific procedure is, of course, necessary before such tests can be considered of diagnostic significance. Several aspects of these tests should give pause to serologists and physicians alike, for they promise to cause serious errors, both of omission and of commission, in the diagnosis and treatment of syphilis.

The first criticism concerns nomenclature. Not merely does no laboratory test yet devised "exclude" syphilis, but no laboratory test even excludes the presence of serum reagin. Moreover, it is not necessarily true that a serum giving a negative Kline exclusion or Kahn presumptive result will be negative by every other technic used. In any extended series of tests, certain syphilitic serums are detected only by an ordinarily less sensitive procedure. These paradoxical results are particularly common when both a flocculation and a complement fixation test are used. Finally, the flocculation phenomenon is peculiarly susceptible to zone reactions, i. e. false negative results caused by the presence of excessive amounts of reagin. A serum may be negative with any flocculation test, screen tests included, when tested as whole serum, yet the complement fixation test may be clearly positive and the flocculation procedure may be similarly positive if the serum is tested in 1:10 or 1:20 dilutions. For these several reasons it is clear that the term "exclusion" test is misleading. It would seem preferable to call these procedures "screen" tests, for such they are, and thus to avoid the present confusing terminology.

A far more important criticism applies not to the tests but to the manner in which they are used. Certainly it was not the intention of their originators that these tests were to be used as diagnostic measures, yet reports as difficult to evaluate as "exclusion test positive, diagnostic test doubtful," presented without explanation to the physician, invite the possibly mistaken diagnosis of syphilis. In the hands of experts these exclusion procedures may be highly specific. In the average laboratory they are often not specific, and experience has shown a general average of false positive reactions ranging from 1 to 10 per cent. When a laboratory obtains a positive "exclusion" or "presumptive" result, the burden of proof rests on the laboratory that such a result is not due to laboratory error but reflects the actual presence of reagin.

Indeed, one might properly insist that the clinician be not informed of the result of a hypersensitive screen test unless it is negative, for the weeding out of negative serums is its only proper function. No matter what result is obtained when a positive or doubtful screen test is checked by one or more specific diagnostic tests, only the latter should be reported by the laboratory, and the result of the "exclusion" or "presumptive" test should be withheld. The objection may be raised that a report "exclusion test positive, diagnostic test negative" is a valuable guide to treatment in cases of known syphilis and that such a result indicates the persistent presence of traces of reagin. That point of view is debatable. To the extent that the "exclusion" test may be false, it may be as much in error with syphilitic serums as with nonsyphilitic serums. More important, antisyphilitic treatment is not directed against the presence of serum reagin, it

³⁸ "Presumptive," "Exclusion" and "Screen" Tests for the Serodiagnosis of Syphilis, editorial, J A M A **112** 541 (Feb 11) 1939

is directed against the spirochete. The modern treatment of syphilis properly pays little heed to the serologic response and more to the patient.

Used solely as an intralaboratory procedure to facilitate the recognition of negative serums, the hypersensitive screen test may fill a useful function, but to report positive or doubtful screen tests to the physician as quasidiagnostic tests which he must weigh and interpret cannot fail but cause confusion and invite the mistaken diagnosis of syphilis.

Provocative Test—Barnett, Kulchar and Jones³⁹ attempt to show that the so-called provocative effect following the injection of neoarsphenamine is an unreliable aid to the diagnosis of syphilis. In an earlier paper⁴⁰ the authors describe a method, using the Kline diagnostic test, for the detection of reagin in normal serum. They employed the same technic to determine the provocative effect of neoarsphenamine, 0.45 Gm., in normal and syphilitic persons. Thirty-two normal persons were tested, none of whose serums contained more than 1 unit of reagin (by the quantitative measuring device of the authors) before neoarsphenamine was given. After twenty-four hours the reagin content had increased to 2 units or more in all but 5, in forty-eight hours all but 1 serum showed an appreciable increase in reagin, and in ninety-six hours even this serum had a reagin titer of 3 units. The same procedure was carried out on serums from 30 patients who were being treated for syphilis. Nine of the serums showed no increase in reagin titer. The mean increase in the reagin content of the serums of the nonsyphilitic group was 1 unit, the mean increase in the syphilitic group was 1.3 units. The authors conclude

since the injection of neoarsphenamine produces an increase in reagin-like substance in nonsyphilitic sera, the provocative reaction is an unreliable procedure and a positive reaction should not be considered diagnostic of syphilis.

Biologic False Positive Serologic Reactions in the Presence of Infectious Mononucleosis, Respiratory Infections, Relapsing Fever, Tuberculosis and Malaria—In the early years of the Wassermann test many diseases other than syphilis were said to give occasionally or often biologic false positive serologic reactions. Later, for two decades or more these statements were discounted except in regard to yaws, leprosy and perhaps malaria. Still more recently evidence is accumulating which indicates that the early opinion was correct and that conditions other than syphilis may provide false positive results.

39 Barnett, C. W., Kulchar, G. V., and Jones, R. B., Quantitative Provocative Reactions in Normal and Syphilitic Sera Following the Injection of Neoarsphenamine, *Am J Syph, Gonorr & Ven Dis* **22** 712 (Nov) 1938.

40 Barnett, C. W., Jones, R. B., and Kulchar, G. V., Measurement of Reagin in Nonsyphilitic Sera, *Proc Soc Exper Biol & Med* **33** 214 (Nov) 1935.

Bernstein ⁴¹ found that transitorily positive complement fixation or flocculation or both developed in 6 of 37 personally observed cases of infectious mononucleosis, and Sadusk ⁴² observed the same phenomenon in 3 of 37 cases of this disease

Krag and Lønberg ⁴³ point out that when the specificity of a given serologic test is under determination, generally by the selection of samples of serum from a group known to be syphilitic and a group that is nonsyphilitic, the test proves to be remarkably specific, but that when it is put into routine use, with all types of disease being encountered, nonspecificity is often revealed. Of 120,000 specimens of serum from nonsyphilitic patients which were tested in the Danish Serum Institute over a period of eighteen months, 53 (0.04 per cent) gave biologic false positive results. Of the 53 serums giving false positive results, 60 per cent were from patients with respiratory infections. As causes of these false positive reactions the following diseases are listed: pneumonia 14, bronchitis 6, pleurisy 1, pulmonary tuberculosis 2, sore throat 3, otitis media 2, common cold 1, emphysema 1, herpes genitalis 5, rat bite fever 2, malaria 1, gonorrheal pelvic disease 5, torqued uterine fibroma (?) 1, unidentified disease 9.

Chung and Chang ⁴⁴ found that 7.95 per cent of 88 patients with relapsing fever had biologic false positive blood tests for syphilis. The cerebrospinal fluid of 16 of these patients was examined from two to four times, and that of 9 gave a positive Wassermann reaction, within one to three weeks after the temperature of these 9 patients became normal, the reaction of their spinal fluid reverted to negative. Murrell ⁴⁵ reports a case of relapsing fever in which the serologic test for syphilis was positive. The patient was given four doses of mapharsen (hemialcoholate of 3-amino-4-hydroxyphenylarsine oxide hydrochloride), which cured the relapsing fever, and the serologic tests promptly became negative and remained so.

Parran and Emerson ⁴⁶ analyzed the serologic results reported for 450 nonsyphilitic patients with pulmonary tuberculosis. All the serums

41 Bernstein, A. False Positive Wassermann Reactions in Infectious Mononucleosis, *Am J M Sc* **196** 79 (July) 1938

42 Sadusk, J. F. Temporarily Positive Kahn and Wassermann Reactions in Infectious Mononucleosis, *J A M A* **112** 1682 (April 29) 1939

43 Krag, P., and Lønberg, A. The Occurrence of Strong Non-Specific Wassermann-Kahn Reactions, *Acta dermat-venereol* **19** 612 (Dec) 1938

44 Chung, H. L., and Chang, F. C. Relapsing Fever. Clinical and Statistical Study of Three Hundred and Thirty-Seven Cases, *Chinese M J* **55** 6 (Jan) 1939

45 Murrell, T. W. Positive Wassermann Reaction in Spirochetal Infections Other Than Syphilis, *Arch Dermat & Syph* **39** 667 (April) 1939

46 Parran, T., and Emerson, K. The Effect of Tuberculosis on Serologic Reactions for Syphilis, *Am Rev Tuberc* **39** 1 (Jan) 1939, *Ven Dis Inform* **20** 1 (Jan) 1939

were tested with the Eagle macroflocculation test, the Kline, Kahn and Hinton flocculation tests, and the Kolmer and the Eagle complement fixation tests. Positive or doubtful results were reported with from one to three of these tests for 26 (7.8 per cent) of the 450 patients, none of the 26 gave doubtful or positive results with more than three of the tests employed. The authors conclude

inasmuch as with the present serologic tests for syphilis both typical and atypical false doubtful and false positive results are found in serums from tuberculous donors, it is evident that tuberculous toxemia may contribute a confusing factor to syphilis serology. It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures.

Kitchen, Webb and Kupper⁴⁷ inoculated 30 nonsyphilitic persons with malaria. Specimens of blood were collected before inoculation, during the incubation period, during paroxysms and for a considerable period after the termination of the malaria. Each patient in whom malaria developed showed a positive serologic reaction for syphilis at some time between inoculation and a date fourteen days after the termination of the attack. In 72 per cent of the cases the positive reaction first appeared during the third and fourth week after inoculation. Positive reactions were observed in a few instances before clinical symptoms of malaria developed. In 68 per cent of the cases the positive reactions appeared during the first two weeks of the febrile period. The percentage of positive reactions was highest during the period from fifteen to twenty-one days after the last paroxysm. The duration of the positive serologic reactions exceeded three weeks in 60 per cent and four weeks in 48 per cent of the cases. This work confirms the work of Ester,⁴⁸ who found that in 9 of 10 cases of inoculation with malarial parasites serologic tests for syphilis became positive.

False Positive Reactions of Cerebrospinal Fluid in Tests for Syphilis—McLean and Munger⁴⁹ report 10 cases in which cerebrospinal fluid gave biologic false positive reactions in tests for syphilis. The diagnoses in these cases were as follows: encephalomalacic atrophy, encephalomalacia, streptococcic septicemia, electrical burn, extrathelial panniculitis, cerebrospinal rhinorrhea, skull fracture, concussion, neuritis and multiple

47 Kitchen, S. F., Webb, E. L., and Kupper, W. H. The Influence of Malarial Infection on the Wassermann and Kahn Reactions, *J. A. M. A.* **112** 1443 (April 15) 1939.

48 Ester, F. Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, *Gior. di batteriol. e immunol.* **17** 502 (Oct.) 1936.

49 McLean, A. J., and Munger, I. C., Jr. False Positive Wassermanns in Cerebrospinal Fluid, *West J. Surg.* **46** 455 (Sept.) 1938.

sclerosis These authors experimentally produced a positive Wassermann reaction in the cerebrospinal fluid of a dog by injecting intracisternally the fluid from a craniopharyngioma

Positive reactions of spinal fluid in tests for syphilis have been reported in the past for patients who had spontaneous malaria Kuske⁵⁰ investigated the frequency with which complement fixation tests for syphilis with cerebrospinal fluid from patients being given malaria treatment for gonorrhea became positive He was unable to demonstrate positive reactions of the spinal fluid from any of these patients He also noted that positive Wassermann reactions did not develop in the spinal fluid of patients with latent syphilis during malarial infection

PUBLIC HEALTH ASPECTS

Probability of Acquiring Syphilis and Frequency of a Disastrous Outcome—In an important paper Vonderlehr and Usilton⁵¹ present the

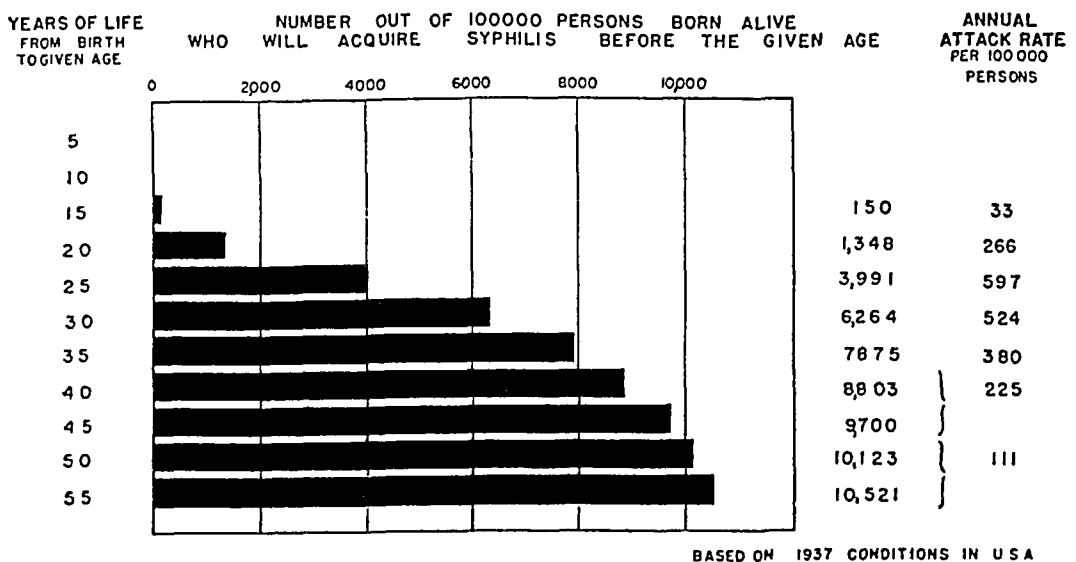


Fig 1—Schema showing that the number of persons acquiring syphilis during life is 1 in every 10 (after Vonderlehr and Usilton⁵¹)

statistical data which justify the statement that “syphilis strikes one out of every ten adults”

This statement is based on the annual attack rate [based on those found in surveys of licensed treatment sources within the past two years] applied to 100,000 individuals born alive and followed throughout life Although the annual attack rate seems low, when cumulated so as to indicate the probability of acquiring syphilis by a given age, it is found that 10,000 people before the attainment

50 Kuske, H Zur Beurteilung der Luesreaktionen im Serum und im Liquor cerebrospinalis bei Impfmalaria, Dermat Ztschr **78** 137 (Aug) 1938

51 Vonderlehr, R A, and Usilton, L J Chance of Acquiring Syphilis and the Frequency of Its Disastrous Outcome, New York State J Med **38** 1376 (Nov 1) 1938, Ven Dis Inform **19** 396 (Nov) 1938

of the fiftieth year of life will have acquired syphilis out of every 100,000 born alive

This rate is different from that found on routine serologic examination of persons tested under the antenuptial physical examination laws, in industry, or in any random sample of the population. Several reasons for these differences are given: (a) Many persons in a random sample are still in danger of acquiring the infection, (b) The blood test for syphilis becomes negative either spontaneously or as the result of treatment in many infected persons, (c) Death removes from the population a high proportion of those who are infected.

As to a disastrous outcome of syphilis, Vonderlehr and Usilton present data to show that treatment decreases this probability, especially as to cardiovascular and neurosyphilis, and (an observation important

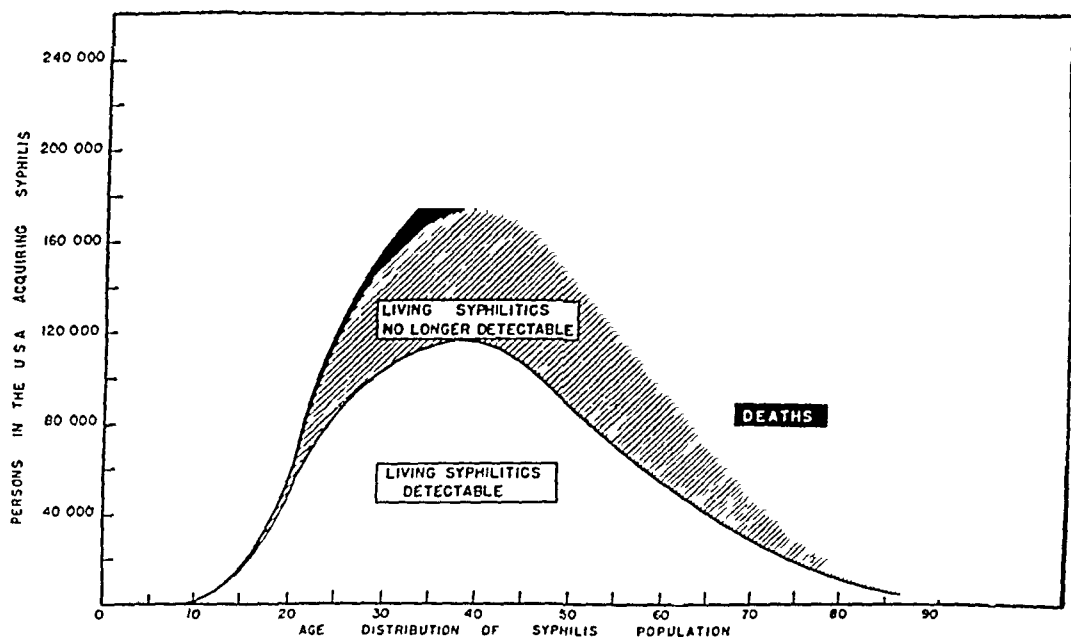


Fig 2—Schema showing factors which reduce the number of persons with detectable syphilis to 1 in 100 (after Vonderlehr and Usilton⁵¹)

to public health officer and clinician alike) that a satisfactory result from the treatment of early syphilis which has been maintained for from three to ten years after treatment is practically certain to be maintained further over a ten to twenty year period.

Syphilis Control in the South—Vonderlehr⁵² calls attention to the magnitude of the problem of syphilis in the southern half of the United States and the relative lack of clinics and clinical equipment. Of the 518,000 persons estimated to acquire syphilis annually, 65 per cent are in sixteen southern states and the District of Columbia, though only 30 per cent of the population lives in this area. The medical facilities

⁵² Vonderlehr, R. A. The Control of Syphilis in the Southern States, *South M J* **31** 863 (Aug) 1938.

so far available in these southern states provide for only about 20 per cent of the medical care needed for the effective control of syphilis. In contrast to this gloomy picture, Sharp⁵³ describes progress in the South. Eleven of these sixteen states now have full time officers for the control of venereal disease. Ten states distribute antisyphilitic drugs free to the indigent, and two of these states distribute drugs to all patients. In twelve states laboratory facilities for direct and indirect dark field examination are now available. In all states but one, free serologic tests are performed. Efforts are being made to increase epidemiologic investigation and to train health officers, public health nurses, venereal disease control officers and cooperating clinicians.

Syphilis Control in the City of New York—Rice,⁵⁴ commissioner of health of the city of New York, discusses the problem of syphilis control in general and outlines the basic principles followed by the New York City Health Department.

The chief elements of the program are

- 1 Case finding activities to include
 - (a) Popular education
 - (b) Epidemiological investigation
- 2 Easily available diagnostic services for the general population
- 3 Treatment services for low income group
- 4 Follow-up services to retain patients under treatment at least until they are noninfectious
- 5 Professional education both for practicing physicians and for undergraduate medical students
- 6 Facilities to aid private physicians and clinics in keeping patients under their treatment including
 - (a) Consultation service,
 - (b) Free drugs,
 - (c) Follow-up service

Syphilis in Colleges—Tumbleson and Ennes⁵⁵ investigated the incidence of syphilis in the colleges of the United States by sending questionnaires to the administrative heads of various institutions. Serologic reports were obtained on 83,000 students. Among white students the rate of positive tests was 2.03 per thousand for men and 1.78 per thousand for women. The rate for Negro students was 26 per thousand.

53 Sharp, W. K., Jr. Progress in Syphilis Control in the Southern States, *South M. J.* **31** 866 (Aug.) 1938.

54 Rice, J. L. Syphilis and Gonorrhea as Public Health Problems, *Ann. Int. Med.* **12** 503 (Oct.) 1938.

55 Tumbleson, R. C., and Ennes, H. W., Jr. A Study of Syphilis in American Colleges, *J. Social Hyg.* **25** 184 (April) 1939.

for men and 27.6 per thousand for women. There was no significant difference among colleges in various regions of the country.

Epidemiology of Syphilis—Smith and Sheppe⁵⁶ found a 75 per cent incidence of syphilitic infection among persons who had been in sexual contact with patients suffering from early syphilis.

Clark⁵⁷ insists that before syphilis can be eradicated a concentrated effort must be directed toward the reservoirs of infection. One hundred and twenty-two patients with early syphilis named 168 persons with whom they had been in sexual contact, of whom 112 (66.8 per cent) were examined. Of these, 63 (56.2 per cent) were found also to have early syphilis. Among 368 family contacts of the 122 patients, 271 (73.5 per cent) were examined and 37 (13.6 per cent) were found to have early syphilis.

Kulchar and Ninnis⁵⁸ determined the source of infection of 1,152 syphilitic patients in San Francisco. Of 909 infected men, 39.8 per cent were infected through contact with prostitutes, 51.1 per cent through clandestine sexual contacts, 4.7 per cent through marital contact and 4.4 per cent through homosexuality. Of 243 infected women, 18.1 per cent were infected through prostitution, 54.3 per cent through clandestine sexual contact and 27.6 per cent through marital contact. The authors feel that from the public health standpoint clandestine sources of infection are relatively more important than prostitution inasmuch as 35 per cent of the prostitutes could be located and put under treatment, whereas only 14 per cent of the clandestine contacts could be traced.

Cost of Caring for Syphilis—Brumfield⁵⁹ has estimated the cost of caring for syphilitic persons in Buffalo in 1936. The population of Buffalo is 573,076, of whom 13,563 are Negroes.

The cost of syphilis (exclusive of the hospitalization of early and latent hospital cases) was \$165,352.21 (\$0.287 per capita), of which \$105,216.21 (\$0.183 per capita) was spent for the hospitalization of patients suffering from late manifestations of the disease.

The cost of operating ambulatory clinics was \$32,834.52 (\$0.058 per capita) and of serologic laboratories \$25,274.90 (\$0.044 per capita). The cost of antisyphilitic drugs was \$1,926.58 (\$0.003 per capita).

A great saving in public funds could be accomplished through case-finding procedures directed toward the placing of patients under treatment in the

⁵⁶ Smith, D. C., and Sheppe, W. M. Studies in the Transmission of Syphilis, West Virginia M. J. **34** 101 (March) 1938.

⁵⁷ Clark, E. G. Fundamentals in the Eradication of Syphilis, South M. J. **32** 460 (May) 1939.

⁵⁸ Kulchar, G. V., and Ninnis, E. I. Sources of Infection in Syphilis, Am. J. Syph., Gonorr. & Ven. Dis. **22** 584 (Sept.) 1938.

⁵⁹ Brumfield, W. A. Hospital, Clinic and Laboratory Costs of Syphilis in Buffalo, New York, with a Comparison of Similar Costs in Baltimore, Maryland, Ven. Dis. Inform. **20** 63 (March) 1939.

early stages of the disease and thus preventing late manifestations. The expenditure of funds for such procedures would undoubtedly be saved many times over.

From a compilation of various statistical data, Rice⁶⁰ concludes that blindness is due to syphilis in about 15 per cent of cases in this country. Usually it is from primary atrophy of the optic nerve. Since the 1930 census enumerated 63,489 blind persons in the United States, there are about 10,000 persons who are blind because of syphilis. Rice estimates that syphilitic blindness alone causes an annual loss of earnings of \$6,000,000 and necessitates special appropriations by taxing bodies and private charity of more than \$4,000,000 additional.

Syphilis and Life Insurance—Murrell and Manson⁶¹ properly object to the present approach of insurance companies to syphilis among applicants, i. e., to the question "Have you ever had syphilis?" Those who admit that they have had the disease are either rejected or must pay an augmented premium, those who deny infection present a possible risk which the company ignores. About 2 per cent of applicants for life insurance have syphilis, but only 0.127 per cent admit that syphilitic infection is present. Those persons who admit that they are infected are given undue publicity. The information not only goes through the hands of many secretaries but is then sent to a central bureau. The authors suggest the following remedy:

(1) Delete the question ["have you ever had syphilis?"] from the blank and go on in entire ignorance. This would not be bad, since at present the companies must be 85 per cent ignorant.

(2) Delete the question and do a routine Wassermann or precipitation test on all applicants for insurance over a certain amount. This would be a complete solution, for a positive serum test is not necessarily proof of the existence of syphilis and is not, therefore, actionable before the courts and its recording would be ethical.

Laws and Syphilis—During the past year there has been much debate, in state legislatures and among physicians, as to laws requiring premarital and prepartum blood tests. Snow⁶² is of the opinion that such laws are useful but must not be introduced too quickly. As of March 1939, ten states required premarital serologic tests, and like bills were pending in the legislatures of thirty-three others. Four states required prepartum serologic tests, and like bills were before the legisla-

60 Rice, E. E. Cost and Loss from Syphilitic Blindness in the United States, *Ven Dis Inform* 20:91 (April) 1939.

61 Murrell, T. W., and Manson, R. C. Syphilis and Life Insurance, *South M J* 32:322 (March) 1939.

62 Snow, W. F. Protection of Marriage and Childlife Against Syphilis, *Am J Syph, Gonorr & Ven Dis* 23:277 (May) 1939.

tures of eighteen others Nelson,⁶³ however, objects to compulsory premarital examination Stokes and Ingraham⁶⁴ take a neutral stand

An editorial⁶⁵ commentator briefly summarizes the arguments in favor of and against premarital laws The arguments in favor are as follows

- 1 They are valuable methods of case finding, the first essential of any syphilis control program
- 2 They will decrease the transmission of syphilis in marriage
- 3 They will decrease the incidence of congenital syphilis
- 4 By insistence on blood tests by "approved laboratories" they will raise the standard of laboratory performance throughout the country
- 5 They will have a general educational value, in keeping the problem of syphilis clearly in the public mind

The arguments against them, equally briefly, are

- 1 In the diagnosis of syphilis, emphasis is laid almost wholly on the laboratory
- 2 The specificity of serologic tests for syphilis in the best of hands (the originators of the tests themselves) is technically short of perfect The recent serologic surveys of the United States Public Health Service and the American Society of Clinical Pathologists point out that (a) in the most competent hands (those of the originators), modern serologic tests provide from 0.2 to 1 per cent technical false positive results in known nonsyphilitic persons, (b) in laboratories other than those of the originators, performance may be as good as this, but an important number of laboratories (including more than one state or municipal health department laboratory), report technical false positive results in normal persons in from 1 to 10 per cent of those tested

3 The specificity of serologic tests for syphilis is not only technically but also biologically short of perfection Several diseases, including two reasonably prevalent in this country (malaria and infectious mononucleosis), cause biologic false positive results in a significant proportion of cases, and far too little positive modern information is available as to biologic false positive tests in many other conditions (e g, vaccinia, after serum treatment, during fever or jaundice, etc)

Moreover, evidence is accumulating to suggest that the blood of a small but as yet unknown proportion of perfectly normal persons may from time to time or permanently contain enough reagin or reagin-like substance to cause a transitory or permanent biologic false positive serologic test

Therefore, in view of the second and third items, a considerable number of nonsyphilitic persons will be caused undue alarm, delay in marriage, and expense in unraveling the significance of false positive or doubtful results The case reports of Stokes and Ingraham make clear that this is already happening, as other consulting syphilologists also can testify

63 Nelson, N A Marriage and the Laboratory, *Am J Syph, Gonorr & Ven Dis* **23** 288 (May) 1939

64 Stokes, J H, and Ingraham, N R, Jr Syphilis and the Law, with Discussion of False Positive Blood Serologic Tests, *J A M A* **112** 1133 (March 25) 1939

65 Premarital and Prenatal Examination Laws for Syphilis, editorial, *Am J Syph, Gonorr & Ven Dis* **23** 386 (May) 1939

4 The blood test is a wholly invalid indicator of infectiousness or noninfectiousness in syphilis

5 Four States (Wisconsin, Illinois, Michigan, and Kentucky) have rushed so headlong into such legislation as to forbid the marriage of a person with a positive serologic test for syphilis at any time, regardless of his actual or potential infectiousness. Their hasty, misguided, and unjust legislative example may be followed by other states

6 Where the law requires blood test evidence to be reinforced by clinical examination, it is even more faulty, since, at an estimate, 95 per cent of all patients infected with syphilis will show no gross physical evidence of the disease at the time of life when marriage is usually contracted

7 The law will not serve its purpose in preventing the spread of syphilis within marriage. Premarital intercourse is already so frequent as to make the law an effort to lock the stable door after the horse is stolen. In the social and economic groups having the highest incidence of syphilis, the incidence of common-law marriages and of illegitimacy will be increased

Brunet and Salberg⁶⁶ have analyzed statistically the information as to age, sex life, pregnancies, abortions and venereal disease obtained from 913 women who applied to their clinic for compulsory premarital examinations. Only 177 (19 per cent) of the group were found to have intact hymens. In spite of the large number who had apparently been sexually exposed, only 2 per cent had positive Kahn or Wassermann tests

In Wisconsin, Lorenz⁶⁷ found only 295 persons (0.6 per cent) with positive serologic tests for syphilis among 45,992 examined as a routine under the antenuptial blood test law

Compulsory vs Voluntary Methods in the Control of Syphilis—There is ample evidence of a material decline in the incidence of fresh syphilitic infection in northern and northwestern European countries. For the Scandinavian countries, Holland and Great Britain, the data are documented afresh by a British commission (Harrison and associates⁶⁸) and for Russia in a striking paper by Danyushevsky⁶⁹. Harrison and the British committee were especially interested in the trends in the

66 Brunet, W. M., and Salberg, J. B. The Findings in Nine Hundred and Thirteen Premarital Examinations, *Am J Syph, Gonorr & Ven Dis* **23** 300 (May) 1939

67 Lorenz, W. F. Antenuptial Blood Tests in Wisconsin, *Wisconsin M J* **38** 318 (April) 1939

68 Harrison, L. W., Ward, D. C. L., Ferguson, T., and Rorke, M. Report on Anti-Venereal Measures in Certain Scandinavian Countries and Holland, Ministry of Health Reports on Public Health and Medical Subjects, no. 83, London, His Majesty's Stationery Office, 1938

69 Danyushevsky, S. M. Combating Venereal Diseases in the U. S. S. R., *Am J Syph, Gonorr & Ven Dis* **23** 498 (July) 1939

several countries studied because of differences in public health technique. They conclude

Considering that in the countries employing compulsory treatment [the Scandinavian countries] and in those which rely on a voluntary system [Holland, England and Wales, Scotland] the degree of success in reducing the incidence of syphilis and of relative failure in gonorrhea are broadly similar, compulsory treatment does not seem to us to be a major factor influencing the results of the anti-venereal measures in the countries where it is employed

Harrison and his group believe that the fall in the incidence of syphilis is a direct reflection of the provision of adequate facilities for treatment and that such compulsory factors as legal insistence on treatment, on examination of contacts or of other members of the family (the epidemiologic approach to case-finding now so popular in the United States), on routine serologic testing or even on organized follow-up service, are relatively noncontributory

In a lengthy but important article Towne⁷⁰ analyzes Harrison's British report. He points out that the statistical basis for a comparison between the figures for the incidence of syphilis in the several countries is inadequate and that certain of the statistical methods employed by the British committee may be invalid. He concludes that

Both compulsory and voluntary methods are needed. Each patient should, so far as possible, be dealt with on an individual basis through a friendly, educative, suasive approach. Clinics and also private practitioners should have the services of public health nurses, medical social workers, or other qualified field workers. Modern epidemiologic methods of finding sources of infection and new cases should be utilized. Public health authorities should maintain complete and intelligently analyzed statistical information concerning these diseases, both en masse and in respect to the relative effectiveness of different methods of control. To this end and for other purposes as well, the official reporting of all cases of syphilis and gonorrhea should be made mandatory. There should also be needed legal authority for the proper use, when and as necessary and particularly in cases of uncooperative patients, of compulsory measures concerning the carrying out of treatment and the prevention of new infections.

These and many other of the myriad papers of the past few years on public health measures for the control of syphilis raise an exceedingly interesting speculative problem. For public health authorities in the United States the model, on which their efforts are patterned, is found in Scandinavia and especially Sweden, where fresh syphilitic infections have fallen to a very low level. There has been a universal tendency to apply *post hoc ergo propter hoc* reasoning here, to wit: "Certain countries have adopted certain measures for the control of venereal disease, in these countries the incidence of syphilis has markedly decreased,

70 Towne, A. W. Compulsory Versus Voluntary Methods of Venereal Disease Control in Scandinavia, Holland, and Great Britain, *Am J Syph, Gonorr & Ven Dis* 23:348 (May) 1939.

therefore the decrease is directly due to the measures adopted." But, in a very large sense, this reasoning is faulty and uncontrolled. In practically all countries of the world except Sweden and Denmark there is a lack of accurate data as to the incidence of syphilis over a long period. Particularly is there a lack of worth while information as to the incidence or trend of syphilitic infection in various Southern and Southeastern European or in North or South American countries, where (at least until recently) there has been no organized effort at the control of syphilis. Where many control measures are simultaneously employed, it is impossible to evaluate the effect of any one.

The available figures for the world as a whole at least suggest that the incidence of syphilis may be declining, and possibly at the same relative rate in those countries which have not made a major public health effort as in those which have, and that the decline may be due not to the measures adopted for its control but to natural phenomena not as yet understood. This critical comment is not in the least intended to decry the present effort in this country to stamp out syphilis or to imply that it will not be successful, it is fair to assume that if the decline in syphilis in, e. g., Sweden has actually been due to the control measures adopted, those same methods or appropriate modifications of them will produce the same result in the United States. It is, however, suggested that in most countries, including this one, morbidity and mortality statistics do not yet permit sweeping conclusions as to the efficacy of control procedures.

DRUGS

Action of Arsphenamines and Bismuth Compounds in Vitro—There is now accumulating important information as to the action of anti-syphilitic drugs. Since the time of the discovery of arsphenamine it has been thought that the action of this drug on *S. pallida* was indirect. Since arsphenamine was thought not to kill spirochetes in vitro, it was postulated that the drug was converted in vivo into an actively spirocheticidal substance. Eagle⁷¹ has restudied the problem and has demonstrated that arsphenamine, neoarsphenamine, silver arsphenamine and arsenoxide are spirocheticidal in vitro. Varying dilutions of these drugs were added to an emulsion of rabbit chancre and were found in individual experiments to immobilize *S. pallida* in dilutions approximating 1:250,000 for neoarsphenamine, arsphenamine and silver arsphenamine and 1:1,000,000 for arsenoxide. The spirocheticidal property of the drugs in these dilutions was found to be affected by (1) the length of time the drug remained in contact with the emulsion (the longer the interval the higher the drug's effectiveness), (2) the tempera-

71 Eagle, H. On the Spirocheticidal Action of Arsphenamines on *Spirocheta Pallida* in Vitro, *J. Pharmacol. & Exper. Therap.* **64**: 164 (Oct.) 1938.

ture (the higher the temperature within the range of 23 to 37 C [73.4 to 98.6 F] the more organisms killed and the shorter the period required), and (3) the addition of tissue derivatives, which inhibited the *in vitro* spirocheticidal action. Serum has only a slight inhibitory effect.

The action of bismuth in syphilis has been as poorly understood as that of arsenic, and, like arsenic, bismuth has been thought not to be directly spirocheticidal. Levaditi⁷² attributed its action to the formation *in vivo* of a hypothetical bismuth-protein complex, "bismoxyl." Kolle and Evers,⁷³ on the other hand, presented evidence that bismuth is not actively spirocheticidal even *in vivo* and that it merely inhibits the growth of *S. pallida*. Now, however, Eagle⁷⁴ shows that, like arsenic, bismuth is probably directly spirocheticidal. He says:

It would appear from the experiments here described that bismuth compounds kill pathogenic *Sp. pallida in vitro*. The organisms are immobilized, become non-infectious for rabbits, and are presumably dead. There was no indication that tissue derivatives contributed in any way to the antispiochetal action of bismuth, on the contrary, as in the case of the arsphenamines, tissue extracts regularly and markedly inhibited this activity. As much as an eighty-fold decrease in the apparent efficacy of a bismuth preparation could be produced by increasing the concentration of tissue extracts.

Two of six soluble bismuth preparations commercially available formed precipitates on addition to serum or tissue extracts, their activity *in vitro* was correspondingly impaired. The remaining four preparations were approximately $\frac{1}{4}$ to $\frac{1}{28}$ as active as "arsenoxide," the bismuth and arsenic being compared on a molar basis in each instance. The possibility must therefore be considered that bismuth compounds act neither as catalysts, inhibitors, nor precursor substances, but that the therapeutic action of bismuth in syphilis depends in part, and perhaps primarily, on its direct spirocheticidal action on *Sp. pallida*.

In a later paper Eagle⁷⁵ shows that the concentrations in which arsenoxide, arsphenamine, neoarsphenamine and bismuth destroy *S. pallida in vitro* are comparable to the concentrations obtainable in the human body with the usual therapeutic doses. Arsenoxide is spirocheticidal in dilutions of 1:650,000 to 1:4,700,000 when mixed *in vitro* with edema fluid from a rabbit chancre and allowed to remain

72 Levaditi, C., and Howard, A. Activation des propriétés curatives du bismuth dans la syphilis sous l'influence de tissus riches en glutathion, *Compt rend Soc de biol* **100** 469 (Feb. 22) 1929.

73 Kolle, W., and Evers, E. Experimentelle Untersuchungen über Syphilis und Rekurrensspirochätose. III. Experimentelles über Syphilisinfektion ohne Symptome, *Deutsche med Wchnschr* **52** 557 (April 2) 1926.

74 Eagle, H. On the Spirocheticidal Action of Bismuth Compounds on Pathogenic Spirocheta Pallida *in Vitro*, *Bull Johns Hopkins Hosp* **63** 305 (Nov.) 1938.

75 Eagle, H. The Minimal Effective Concentration of Arsenic and Bismuth Compounds on *T. Pallidum in Vitro* in Relation to the Therapeutic Dose, *Am J Syph, Gonorr & Ven Dis* **23** 310 (May) 1939.

at room temperature from one and one-quarter to two and one-half hours. Arsphenamine, neoarsphenamine and silver arsphenamine are likewise effectively spirocheticidal in dilutions of 1:250,000 to 1:1,250,000. Water-soluble bismuth preparations are spirocheticidal in dilutions of 1:50,000 to 1:225,000. If 0.4 Gm of arsphenamine, 0.05 Gm of arsenoxide or an amount of a bismuth compound containing 0.04 Gm of bismuth metal is injected into a patient weighing 70 Kg, these doses should represent concentrations in the body fluids, if the drugs are evenly distributed throughout, of 1:100,000, 1:800,000 and 1:1,000,000, respectively. This concentration obtainable for the arsenicals is sufficient to be directly spirocheticidal *in vivo*.

The agreement between the bismuth concentrations actually attained in the circulating blood and organs and the experimentally determined effective concentrations *in vitro* is surprisingly good, and constitutes strong evidence for the thesis that the therapeutic effect of bismuth in syphilis rests on a direct spirocheticidal action similar to that observed in the test tube.

Carrying further his studies of the action of the arsenicals and heavy metals, Eagle⁷⁶ presented papers before the American Society of Pharmacology and Experimental Therapeutics which have so far been published only in abstract, the detailed experiments to follow. Here he shows that

The antispirochetal action *in vitro* of "arsenoxide" (m-amino-p-hydroxyphenyl-arsenoxide) and bismuth compounds was unaffected by the removal of molecular oxygen [from the spirochete-arsenical mixture] and is probably due to these compounds as such. In marked contrast, neoarsphenamine, which is highly spirocheticidal when dissolved aerobically, was negligibly so when dissolved and tested under nitrogen in the absence of oxygen. Its relatively marked antispirochetal action when tested aerobically (25 to 60 times that observed under nitrogen) is apparently due to its oxidation by molecular oxygen to other directly spirocheticidal compounds. This oxidation did not require the presence of tissue derivatives and proceeded so rapidly that solutions became actively spirocheticidal within 3 to 5 minutes.

Commercial arsphenamine and silver arsphenamine were intermediate between arsenoxide and neoarsphenamine, in that although $\frac{3}{8}$ to $\frac{7}{8}$ of their antispirochetal activity *in vitro* was due to oxidation products, there was a small but significant residual activity in the absence of oxygen. In the case of arsphenamine, a large part of this residual activity was accounted for by "arsenoxide" or by "arsenoxide"-like substances present as an impurity.

Sulfhydryl compounds (cysteine, glutathione, and thioglycollic acid) added in sufficient excess to arsphenamines, "arsenoxide," bismuth, or mercury compounds, almost completely abolished their antispirochetal action *in vitro*. The large excess which was necessary to cause complete inactivation of the arsenical suggests that the addition compound may be readily hydrolyzed. Thiamin chloride and methionine, which contain a —S— rather than a —SH group, had no inhibitory effect.

⁷⁶ Eagle, H. The Effects of Molecular Oxygen and Sulfhydryl Compounds on the Antispirochetal Action of Arsenic, Bismuth and Mercury Compounds *In Vitro*, J. Pharmacol. & Exper. Therap. **66** 10 (May) 1939.

These findings are of interest in relation to the thesis that the antispirechetal action of arsenic, bismuth, and mercury compounds may rest on their common affinity for sulfhydryl groups in the *T pallidum*

Neoarsphenamine — Probey and Harrison ⁷⁷ find that the instability of neoarsphenamine due to heat increases directly with the moisture content of the drug

Solusalvarsan — This drug (3,4-diacetylamino-4-hydroxyarsenobenzene-2-sodium glycocholate), well known in Germany, has been little used in this country. It is said to have two advantages over other arsphenamines: it does not become oxidized when exposed to air, and it may be administered by the intramuscular route. Wendlberger and Hrad ⁷⁸ report the results of treatment of 159 patients with this drug. To 90 patients it was given twice weekly by the intramuscular route in a dose of 0.4 to 0.5 Gm. Seventeen of the 90 patients so treated reacted with dermatitis, of whom 5 had erythema of the ninth day, 6 late erythema, either morbilliform or scarlatiniform, and 6 severe exfoliative dermatitis. Among 69 patients treated intravenously, 3 had erythema of the ninth day, 5 late erythema and 2 exfoliative dermatitis. Aside from causing these cutaneous reactions the drug was satisfactory in the treatment of primary, secondary, late and congenital syphilis. There was reversal of the serologic test in 33 per cent of the cases in which this drug was used in treatment.

Mapharsen — Astrachan and Wise ⁷⁹ used mapharsen in the treatment of 118 patients who had latent syphilis and studied the clinical and serologic effect. In many patients there was disappearance of various symptoms. The serologic response was favorable in 65 of the 101 patients investigated. Fifteen patients whose serologic reactions did not improve were later found to have neurosyphilis. Twenty-eight of the 118 patients experienced some type of reaction to the treatment. Of these, many had mild gastrointestinal disturbance, 7 suffered from intense pruritus, 2 from urticaria, 1 from purpura, 1 from herpes zoster, 7 from erythematous eruptions and 1 from a fixed dermatitis. In only 5 of the 28 instances of reaction was it necessary, however, to discontinue the use of the drug.

Phillips and Knoepp ⁸⁰ found neither improvement nor activation of tuberculous lesions in 34 syphilitic patients treated with mapharsen.

⁷⁷ Probey, T. F., and Harrison, W. T. The Effect of Artificial Temperatures on Stability of Neoarsphenamine, *Pub. Health Rep.* **54** 228 (Feb. 10) 1939.

⁷⁸ Wendlberger, J., and Hrad, O. Zur Verträglichkeit und Wirksamkeit des Solu-Salvarsans bei Luetikern, *Dermat. Wchnschr.* **108** 125 (Feb. 4) 1939.

⁷⁹ Astrachan, G. D., and Wise, F. Further Experiences with Mapharsen. Its Use in Latent Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **22** 470 (July) 1938.

⁸⁰ Phillips, J. R., and Knoepp, L. F. Control of Syphilis in Tuberculosis, *South. M. J.* **31** 1295 (Dec.) 1938.

Acetarsone —Robinson and Robinson ⁸¹ analyze the results obtained in 32 adult syphilitic patients treated orally with acetarsone. Two patients had primary syphilis, with positive serum reactions, 23 patients had moist secondary lesions, and 7 had latent syphilis. The dose was 1 to 3 Gm daily. One gram of acetarsone will not cause disappearance of *S. pallida* from surface lesions, but 2 Gm causes the disappearance of the organisms in twenty-four hours. The serologic tests for syphilis became negative in only 4 of the 25 cases of early syphilis. The incidence of reactions from the drug was so high as to preclude its further use. Of the 32 patients, 4 reacted with dermatitis, 4 with diarrhea, 3 with an increase in the icterus index and 1 with a severe gastrointestinal disturbance. Of the entire group 37.5 per cent had serious reactions.

The use of acetarsone in congenital syphilis will be discussed later.

Bismuth —(a) Oral Administration. There is still little satisfactory experimental or clinical evidence to support the view that orally administered preparations of bismuth are effective in the treatment of syphilis. In a series of papers Hanzlik and associates ⁸² have continued their study of sobisminol. This drug may be given either orally or by intramuscular injection. Administered by either route, it is rapidly absorbed and relatively slowly excreted, producing the desirable combination for efficient antisyphilitic treatment of rapid penetration and sustained circulation of bismuth. Quantities by mouth far in excess of the average therapeutic dose are tolerated by experimental animals, necropsy showing tissue changes to be negligible or absent. The animals, however, show anorexia and loss of weight. The drug causes no appreciable changes in the bones of young white rats.

Shaw, Kemp and Fitzgerald ⁸³ treated 15 syphilitic rabbits orally with sobisminol, 12 of which survived the experiment. Treatment was

81 Robinson, H. M., and Robinson, H. M., Jr. Acid Acetarsone Orally in Treatment of Acquired Syphilis in Adults, *Am J Syph, Gonorr & Ven Dis* **23** 188 (March) 1939.

82 Hanzlik, P. J., Lehman, A. J., and Richardson, A. P. Sobisminol Toxicity, Tolerance and Irritation According to Different Channels of Administration, *J Pharmacol & Exper Therap* **62** 372 (April) 1938. Hanzlik, P. J., and Lehman, A. J. Continued Voluntary Drinking of Sobisminol. General Effects, *ibid* **62** 389 (April) 1938. Hanzlik, P. J., Lehman, A. J., and Richardson, A. P. Excretion of Bismuth After Intramuscular Injection of Sobisminol, *ibid* **62** 404 (April) 1938, Intramuscular Injection of Sobisminol. Absorption and Distribution of Bismuth, *ibid* **62** 413 (April) 1938. Lehman, A. J., and Dock, W. Effects of Drinking Sobisminol on Skeletal Changes in Growing White Rats, *ibid* **63** 88 (May) 1938.

83 Shaw, C., Kemp, J. E., and Fitzgerald, E. M. Sobisminol (Sodium Bismuthate Soluble) in the Treatment of Experimental Rabbit Syphilis, *Am J Syph, Gonorr & Ven Dis* **23** 210 (March) 1939.

given three times a week for five weeks, the weekly dose being that prescribed by Hanzlik, 2199 mg per kilogram measured in metallic bismuth. From one hundred and nineteen to two hundred and thirty-seven days after the conclusion of treatment the popliteal lymph nodes of 6 of the 12 surviving rabbits, on transfer, transmitted the infection to other rabbits. The authors conclude that sobisminol in the doses used is not satisfactory for the treatment of late syphilis in rabbits.

Because of the conflicting reports regarding the value of orally administered bismuth compounds, Stratton⁸⁴ attempted experimentally to determine the amount of bismuth absorbed by measuring the urinary excretion of the element in rabbits. Four bismuth preparations were used, bismutrate (bismuth chloride treated with liver extract), sobisminol, potassium bismuth tartrate and bisiodide. The amount of bismuth excreted in the urine of rabbits following the administration of a single dose of a bismuth compound by mouth, whether containing 20 mg or 200 mg of bismuth metal per kilogram of body weight, was satisfactory for bismutrate and sobisminol, less so for potassium bismuth tartrate and not at all for bisiodide. When fourteen daily doses of a compound containing 20 mg of bismuth metal per kilogram were given, however, there was no proportionate increase in the amount of bismuth excreted, and the daily average amount excreted was far below the level estimated to be necessary for definite antisyphilitic value.

(b) Concentration in Tissues Sollmann, Cole and Henderson⁸⁵ have quantitatively determined at autopsy the content and concentration of bismuth in the viscera of patients who had been clinically treated with preparations of this metal. The concentration of bismuth in viscera is dependent on the total amount of bismuth administered. If one viscus was high in bismuth, all other viscera were proportionately high. Sollmann and Henderson⁸⁶ then quantitatively determined the concentration and the total content of bismuth in the viscera of dogs treated with a single dose of one or another of twelve different bismuth compounds.

84 Stratton, E. K. The Absorption and Elimination of Bismuth Following Its Oral Administration to Rabbits, *Am J Syph, Gonorr & Ven Dis* **22** 728 (Nov) 1938.

85 Sollmann, T., Cole, H. N., and Henderson, K. Clinical Excretion of Bismuth, VII The Autopsy Distribution of Bismuth in Patients After Clinical Bismuth Treatments, *Am J Syph, Gonorr & Ven Dis* **22** 555 (Sept) 1938.

86 Sollmann, T., and Henderson, K. Bismuth Studies VII Bismuth Distribution in Dogs Following Intramuscular Injection of a Single Dose of Various Bismuth Preparations, *Am J Syph, Gonorr & Ven Dis* **22** 738 (Nov) 1938.

Cole, Sollmann and Henderson⁸⁷ give a summary of their experiments as an aid in the choice of a bismuth preparation. They list the commonly used bismuth compounds and recommend the intervals of time at which they should be given in order to maintain a spirocheticidal level of the drug in the blood. Any preparation which furnishes a daily urinary excretion of from 2 to 4 mg. of bismuth is thought to be a valuable antisyphilitic agent. They say

In choosing the bismuth preparation the physician should consider what is indicated in the particular patient

For rapid bismuth effect

Sodium bismuth tartrate in water Injections intramuscularly
three times a week

Sobisminol }
Iodobismitol } Injections twice weekly

If the patient can be persuaded to return twice a week for injections, probably the most efficient preparations in terms of high bismuth excretion are sobisminol and iodobismitol

For a somewhat slower but efficient bismuth effect

Biliposol }
Bismocymol } Injections every five days to
once a week

For an effect slow in building up, but eventually sustained

Injections of oil suspensions of
Sodium potassium bismuth tartrate }
Bismuth subsalicylate } Once weekly

(c) Toxicity, Absorption and Excretion of Bismuth. Kolmer, Brown and Rule⁸⁸ have made a comparative study in lower animals of the toxicity, absorption, excretion and therapeutic effectiveness of thirteen regularly used bismuth compounds. Water-soluble bismuth compounds were more toxic than oil-soluble, and both were more toxic than water-soluble and water-insoluble compounds suspended in oil. In general the water-soluble and the oil-soluble compounds produce nephritis more frequently than the insoluble compounds. The excretion in urine was generally dependent on the rate of absorption and the concentration of the drug in the blood. The water-soluble compounds were excreted more rapidly. The spirocheticidal activity of the compounds was dependent on the amount of elemental bismuth present in

⁸⁷ Cole, H. N., Sollmann, T., and Henderson, K. The Choice of a Bismuth Preparation. Clinical Résumé of Excretion and Retention Studies, Am J Syph, Gonorr & Ven Dis **23** 143 (March) 1939

⁸⁸ Kolmer, J. A., Brown, H., and Rule, A. M. Studies in the Bismuth Therapy of Syphilis. I. A Comparative Study of the Toxicity and Therapeutic Activity of Bismuth Compounds Commonly Employed in the Treatment of Syphilis, Am J Syph, Gonorr & Ven Dis **23** 7 (Jan) 1939

the compound, the chemical structure and the rates of absorption and excretion, and these in turn were dependent on the solubility in the menstruum employed and the solubility in the tissues. The bismuth compounds suspended in oil had by far the highest therapeutic indexes, ranging from 100 to 166. The authors feel that there is an optimum concentration of bismuth in the blood and that this is best obtained by the use of a bismuth compound which is not so rapidly absorbed and excreted as are the water-soluble compounds but which has a relatively high percentage of elemental bismuth and is absorbed and excreted slowly, as are the oil-suspended preparations.

(d) Treatment with Bismuth Compounds in Combination Sollmann, Cole and Henderson⁸⁹ calculated the amount of bismuth excreted in the urine of patients when they were given (1) bismuth subsalicylate in oil alone, (2) bismuth subsalicylate in oil plus iodobismutol and (3) bismuth subsalicylate plus sobisminol. The daily urinary excretion of bismuth after weekly injections of bismuth in oil did not reach 1 mg. before the third week and 2 mg. before the sixth week. However

A graded sequence of injections of soluble bismuth preparations (iodobismutol and sobisminol) with continued weekly injections of bismuth salicylate produces a high initial concentration of bismuth as reflected in the urinary excretion, which reaches at the end of two weeks a level of from 4 to 12 mg. of bismuth a day, according to the drugs used. This concentration then falls so as to join the slowly ascending curve characteristic of salicylate injections about the end of from five to seven weeks, so that the median level does not fall below 2 mg. of bismuth.

The sequence therefore secures the benefit of the intensive action of the water-soluble bismuth preparations in the early part of the course and the advantages of the convenience of salicylate injections in the latter part of the course.

The plan is recommended for use in the treatment of early syphilis, and when arsenic is badly tolerated.

Other Drugs—Pavanati⁹⁰ was unable to demonstrate any spirocheticidal action of four rhodium salts (rhodium chloride, sodium rhodium chloride, potassium rhodium chloride, lithium rhodium chloride) in vitro. However, he treated syphilitic rabbits with these drugs, which were well tolerated whether injected by the intravenous or by the intramuscular route. After one dose of 50 mg. per kilogram the spirochetes disappeared from rabbit syphilomas in twelve to twenty-four hours, the lesions healed rapidly, and there were no relapses. Seven patients with early syphilis were then treated with rhodium chloride, 0.5 Gm. per dose. Spirochetes disappeared from the chancres.

⁸⁹ Sollmann, T., Cole, H. N., and Henderson, K. Combination Courses of Bismuth Administration, *J. A. M. A.* **111** 2175 (Dec. 10) 1938.

⁹⁰ Pavanati, E. Sal di rodio e sifilide (ricerche in vitro, sull' animale e sull' uomo), *Gior. ital. di dermat. e sif.* **79** 837 (Aug.) 1938.

in two to three days, there were no toxic symptoms. There is no record of a follow-up.

Kumasawa⁹¹ found an alkaline solution of lead carbonate to be spirocheticidal but very toxic in rabbits. He then treated 6 syphilitic rabbits with lead acetate, 1 mg per kilogram, injected intravenously, thrice weekly. Three animals died, the other three were "cured" after fifteen to twenty-one injections over a period of five to seven weeks. The drug was used subcutaneously in the same dosage with no deaths and with the same clinical results. Control animals treated at the same time with bismuth compounds were "cured" in a shorter period of time.

UNTOWARD EFFECTS OF TREATMENT

Erythema of the Ninth Day—Cañizares and Thomas⁹² review the literature and report 11 cases of erythema of the ninth day. They feel that this reaction is a clinical entity, clearly distinct from the later appearing edematous exfoliative dermatitis. It may be a response of the autonomic nervous system to arsenic. It does not seem to be influenced by the dose administered, the type of trivalent arsenical, the mode of injection or the spacing of treatments. Blood counts and hepatic function tests gave no definite information. Passive transfer did not demonstrate the presence of antibodies. With proper precautionary measures, subsequent arsenical treatment is usually well tolerated.

Agranulocytosis After Treatment with Neoarsphenamine—Goldberg⁹³ reports a single case confirming the suggestion of Falcone, Epstein and Wever (mentioned in the 1937 review^{1c}) that patients in whom blood dyscrasias develop after treatment with an arsphenamine may nevertheless tolerate mapharsen.

Montanaro⁹⁴ and Lancellotti,⁹⁵ working together, have studied in rabbits and guinea pigs (the former from the pathologic, the latter from the hematologic standpoint) the injury to the blood and blood-forming organs produced by the arsphenamines. While slight evidences

91 Kumasawa, M. Experimentelle Untersuchungen über die antiluetische Wirkung von Bleisalzen, Fukuoka acta med (Abstr. Sect.) **31** 177 (Dec) 1938.

92 Cañizares, O., and Thomas, E. W. Early Acute Arsenical Erythemas. A Study of Eleven Cases of the "Erythema of the Ninth Day" of Milian, Arch. Dermat. & Syph. **39** 867 (May) 1939.

93 Goldberg, M. Mapharsen as a Substitute for Neoarsphenamine in Agranulocytic Angina Following Neoarsphenamine Therapy in a Pregnant Syphilitic Woman, Am. J. Syph., Gonorr. & Ven. Dis. **23** 79 (Jan) 1939.

94 Montanaro, E. Contributo sperimentale alla conoscenza delle lesioni da arsenobenzolo degli organi ematopoietici, Policlinico (sez. med.) **45** 553 (Nov) 1938.

95 Lancellotti, M. Contributo sperimentale alla conoscenza delle lesioni Sanguigne da arsenobenzolo, Policlinico (sez. med.) **45** 573 (Nov) 1938.

of damage were found, the authors were unable to produce a genuine blood dyscrasia

Gastrointestinal Reactions—Irgang⁹⁶ discusses at some length gastrointestinal reactions following the intravenous injection of trivalent arsenicals. He believes that these reactions, the nitritoid crises, arsphenamine shock, dermatitis, thrombopenia, purpura and hepatitis are related to an allergic state

Hemorrhagic Encephalitis—Paley and Pleshette⁹⁷ report another case of hemorrhagic encephalitis following injections of neoarsphenamine in a pregnant woman. In the literature they find reports of 158 cases of hemorrhagic encephalitis. The patients more commonly were males, but of the females who presented this condition, 70 per cent were pregnant. In most instances the complication occurred after the first two or three injections of the arsenical and after a dose of 0.45 Gm. or more.

Relation of Vitamin C to Arsenical Reactions—There is increasing interest in the role played by vitamin C in arsenical dermatitis. Practically all of the literature of the past two years deals with clinical impressions. The few papers describing animal experimentation are confusing, one author believing the lack of vitamin C to be responsible for toxic reactions in animals, and another that excess of vitamin C renders the animal more likely to have reactions. For example, Cohen⁹⁸ feels that before experimental work on the relation of vitamin C to toxic reactions in animals can be regarded as valid, certain basic conditions must be adhered to, namely

- 1 The diet must be adequate in all respects except for vitamin C
- 2 The animal must have sufficient food to avoid starvation
- 3 The ration of vitamin C must be planned upon a sliding scale according to the tooth-protective ration

After fulfilling these conditions, Cohen could find no relationship between the vitamin C content of the diet and sensitivity of the skin to neoarsphenamine.

Karolyi,⁹⁹ however, feels differently about the role played by vitamin C in relation to the toxicity of arsphenamine. He gave to one

96 Irgang, S. Gastric Intolerance Accompanying Arsphenamine Therapy. A Discussion of Its Etiology, Prevention, and Treatment with Case Reports, *Am J Syph, Gonorr & Ven Dis* **23** 241 (March) 1939

97 Paley, S. S., and Pleshette, N. Hemorrhagic Encephalitis in Pregnancy Following Antisyphilitic Therapy with Neoarsphenamine, *Am J Syph, Gonorr & Ven Dis* **23** 69 (Jan) 1939

98 Cohen, M. B. Vitamin C Deficiency. Sensitivity to Neoarsphenamine and Anaphylactic Shock, *J Allergy* **10** 15 (Nov) 1938

99 Karolyi, I. The Effects of Ascorbic Acid and Glycocoll on Chronic Arsenobenzol Poisoning, *Orvosi hetil* **82** 829 (Aug) 1938

series of white rats 25 mg of ascorbic acid and 75 mg of aminoacetic acid daily for ten days, after which he gave arsphenamine in increasing doses, 7 to 40 mg, twice weekly, at the same time continuing to administer ascorbic acid and aminoacetic acid on the day of treatment. A control series was given arsphenamine alone in the same dosage. The animals receiving ascorbic acid lived longer than those receiving arsphenamine alone.

Solvents for the Arsphenamines—In an effort to decrease the incidence of toxic reactions from the arsphenamines, there have been many proposals that a solution of some supposedly detoxifying substance, e. g., dextrose, sodium thiosulphate, aminoacetic acid, various proprietary substances derived from liver (the latter especially in Germany) or one or another vitamin, be used as a solvent for the arsenical drug. A prototype of these studies is described in a paper by Shaw,¹⁰⁰ who used sodium dehydrocholate as a solvent for neoarsphenamine in the effort to prevent gastrointestinal and hepatic reactions. Twelve patients who habitually suffered from nausea and vomiting after receiving neoarsphenamine tolerated the drug well when it was dissolved in a 5 per cent solution of sodium dehydrocholate.

It is unfortunate that, with few if any exceptions, such clinical efforts are unsupported by experimental studies to show that the toxicity of arsphenamine is decreased by the use of the special solvent and, equally important, that if toxicity is decreased, it is not accompanied by a parallel decrease in therapeutic efficiency. Obviously, there is no advantage in the elimination of reactions, especially minor ones, if at the same time the spirocheticidal drug is rendered wholly or partially inert.

Desensitization with Arsphenamine—The consensus is that patients in whom cutaneous sensitivity to the arsphenamines develops cannot be desensitized. Desensitization has often been attempted by the repeated injection of small intravenous or subcutaneous doses. Jacobson and Brill¹⁰¹ describe a new method of desensitization—the intracutaneous injection every other day of 0.15 cc of varying dilutions of arsphenamine. For the first three injections the dilution is 1:1,000,000, for the next two, 1:10,000, for the next two, 1:1,000, and for the eighth and last, 1:100. If there is a marked local or general reaction in the course of these injections, the dose is lowered, or the interval between doses is increased, or both. An average of seventeen to twenty-two

100 Shaw, C. Sodium Dehydrocholate Solution as a Solvent for Neoarsphenamine in the Treatment of Syphilis, *J. Lab. & Clin. Med.* **24**: 624 (March) 1939.

101 Jacobson, A., and Brill, M. The Intracutaneous Method of Desensitizing with the Arsphenamines, *Vestnik venerol. i dermat.* **6**: 49, 1938.

days is required to desensitize a patient. If there is no reaction in the course of the eight intracutaneous injections, therapeutic doses of the drug may be given. Desensitization was attempted with patients. Two patients had exfoliative dermatitis, 3 scarlatiniform eruptions, 3 morbilliform eruptions, 5 urticaria and 1 a fixed dermatitis. Of the 14 patients, 11 were satisfactorily desensitized and could be given therapeutic doses of arsphenamine, 3 could not be desensitized at the first attempt, but 1 of these was desensitized after the described technic had been repeated several times. One of the 2 patients who could not be desensitized was a patient with urticaria, and the other had a fixed dermatitis. The two patients who had exfoliative dermatitis were satisfactorily desensitized.

Unfortunately, it is not certain that all the patients studied were originally sensitized. The American concept of sensitization dermatitis usually does not include scarlatiniform, morbilliform and urticarial eruptions.

Toxicity of Tryparsamide—An editorial commentator¹⁰² says

Tryparsamide (the sodium salt of N-phenyl-glycineamide p-arsonic acid) has been used in the treatment of neurosyphilis and trypanosomiasis since 1923. For a dozen or more years following its introduction, all workers were impressed by the fact that it produced few or no reactions except those involving the optic nerves.

Constitutional reactions from the drug were for many years so rare that Moore, writing in 1933, said "The use of tryparsamide is singularly free from constitutional reactions of any sort. Only two instances of post-tryparsamide jaundice have occurred in our clinic. Dermatitis does not occur after this drug." Stokes, in 1935, mentioned 4 cases of post-tryparsamide jaundice and 3 of dermatitis (all but one from the literature), but he said "I have personally never observed a single significant complication of tryparsamide therapy as such, other than those involving the optic tract."

Within the past few years, however, a distinct change in the reactivity of tryparsamide apparently has occurred. Mild to moderately severe immediate or slightly delayed reactions, such as malaise, chilliness or actual chills, nausea and vomiting, and prostration, formerly completely absent, now seem to occur in a considerable number of cases. The literature since 1933 contains at least 12 direct references to post-tryparsamide jaundice, dermatitis, or other constitutional reactions. Traenkle and Dolce¹⁰³ report two cases of fatal liver necrosis following tryparsamide, and Golz¹⁰⁴ reports a case of severe exfoliative

102 The Toxicity of Tryparsamide, editorial, *Am J Syph, Gonorr & Ven Dis* **23** 389 (May) 1939.

103 Traenkle, H. L., and Dolce, F. A. Acute Fatal Liver Necrosis Following Tryparsamide Administration. A Report of Two Cases, *Am J Syph, Gonorr & Ven Dis* **23** 228 (March) 1939.

104 Golz, H. H. Sensitivity to Arsenical Drugs. Report of an Unusual Case Exhibiting Sensitivity to Both Trivalent and Pentavalent Arsenic, *Am J Syph, Gonorr & Ven Dis* **23** 344 (May) 1939.

dermatitis in a patient previously sensitized to the arsphenamines. In the Johns Hopkins Hospital clinic, to 1936, had occurred 6 cases of post-tryparsamide jaundice (Soffer), an incidence of 0.22 per cent of patients treated, as contrasted to a similar incidence of 0.98 per cent for arsphenamine and 0.63 per cent for neoarsphenamine.

It is noteworthy that practically all of these constitutional reactions, mild and serious, have appeared within the last five years of use of tryparsamide, which for the previous ten years had been nearly or completely free from them. This is a curious and so far unexplained phenomenon of chemotherapy. It has been observed with other antisyphilitic drugs than tryparsamide, and indeed with other compounds than antisyphilitic drugs. Presumably it is due to some slight variation in the raw materials used in drug synthesis or in minor variations which creep into the method of manufacture. These in turn may result either in the presence of traces of impurities or in an end product which, while apparently chemically identical with the original nontoxic product, behaves pharmacologically in a slightly different manner in the human body. In the case of tryparsamide, the increased incidence of constitutional reactions has been a matter of serious concern.

Astrachan and Franks¹⁰⁵ report a typical nitritoid reaction following injections of tryparsamide.

Jaundice from Bismuth—Nomland, Skolnick and McLellan¹⁰⁶ have studied jaundice occurring during antisyphilitic therapy in 75 patients, in 32 of whom they believe the reaction to have been due to bismuth. Of these 32 patients, 10 had received no arsenical, 22 had been given arsphenamine but not for twelve weeks or longer prior to the development of jaundice. Other conditions which might have caused jaundice in these patients were considered and ruled out as probably not responsible. The authors calculated that the probable incidence of bismuth-induced jaundice in their clinic over a period of five years was 1 in 2,242 injections of bismuth compounds, whereas the incidence of arsphenamine-induced jaundice was 1 in 951 injections. Most of these patients were subsequently given further bismuth treatment without recurrence of jaundice.

Lane¹⁰⁷ analyzed the data on 100 patients in whom jaundice occurred during antisyphilitic treatment. Two patients of this group had received no antisyphilitic drugs other than preparations of bismuth. In 8 patients jaundice developed during bismuth therapy more than

105 Astrachan, G. D., and Franks, A. G. Nitritoid Reaction Following an Injection of Tryparsamide, *Arch. Dermat. & Syph.* **38** 949 (Dec.) 1938.

106 Nomland, R., Skolnick, E. A., and McLellan, L. L. Jaundice from Bismuth Compounds Used in the Therapy of Syphilis. Report of Thirty-Two Cases, *J. A. M. A.* **111** 19 (July 2) 1938.

107 Lane, C. G. Jaundice Occurring During the Treatment of Syphilis, *Arch. Dermat. & Syph.* **39** 278 (Feb.) 1939.

twelve weeks after the last dose of an arsenical Lane likewise feels that bismuth may be a cause of jaundice

PATHOLOGIC OBSERVATIONS

Bell¹⁰⁸ estimates the frequency with which pathologic evidence of syphilis was encountered among 27,872 postmortem examinations in Minneapolis hospitals He points out that obvious anatomic evidence of syphilis is less frequent than the positive serologic test, but unfortunately he has made no attempt to correlate clinical findings with observations made at necropsy His data do not, therefore, answer the important questions What is the probable mortality from syphilis if the patients are untreated? If they are treated, what are the effects of varying amounts and kinds of treatment? Syphilis was observed in 2.77 per cent of the 27,872 necropsies and was shown to be the direct cause of death in 2.5 per cent Among infants congenital syphilis, and among adults cardiovascular syphilis and neurosyphilis, accounted for the large majority of deaths from syphilis Especially interesting is the fact that in the fourth decade of life, in which the general death rate is low, syphilis accounted for 8 per cent of the deaths among men

EARLY SYPHILIS

Diagnosis—Clinicians have long been aware that simultaneous infection with gonorrhea and syphilis might occur, the latter being either symptomless or represented by an intraurethral chancre masked by the gonorrheal discharge Friedman¹⁰⁹ describes a simple method by which a purulent urethral discharge may be satisfactorily examined for *S. pallida* The discharge is drawn up into a fine capillary tube about 12 cm long One end is sealed by flame, and the tube is then centrifuged at low speed, 1,000 revolutions per minute, for ten minutes, which removes cellular debris and leaves *S. pallida*, if present, in the supernatant fluid The tube is broken just above the level of the cells and the clear fluid examined by dark field This method was applied in 40 cases of acute gonorrheal urethritis In 37 the results were negative, and subsequent physical examination and serologic tests did not indicate syphilitic infection In another case, no spirochetes were found in the urethral discharge, no primary syphilitic lesion could be found in the patient, and the first serologic tests for syphilis were negative, but fifty-two days later such tests were positive In the remaining 2 cases, *S.*

108 Bell, E. T. Frequency with Which Syphilitic Lesions Are Encountered in Postmortem Examinations, *Arch. Path.* **26**: 838 (Oct.) 1938

109 Friedman, L. A Method for the Darkfield Examination of Pus for *Spirocheta Pallida*, *J. A. M. A.* **112**: 134 (Jan. 14) 1939

pallida was found in the urethral discharge with the technic described. The method was also applied in a case of a penile lesion which bled freely. *S. pallida* was easily demonstrated after, though with considerable difficulty before, centrifugation.

In an article which deserves wide reading by clinicians and public health officers alike, Chambers and Scholtz¹¹⁰ reiterate the advantages of diagnosing syphilis in the primary stage and point out why the results from the use of the dark field microscope are an incomplete solution of the problem of early diagnosis. The reasons are (1) The physician needs special equipment and training, (2) it is difficult to obtain a proper specimen, (3) the patient objects to going to a public diagnostic laboratory, and (4) there are small chances of success with old and locally treated lesions. They believe that many of these difficulties may be obviated by routine biopsy of tissue removed from the edge of the suspected lesion, sectioned and stained by the method described by Krajan.⁸ The practical advantages of this method are: The staining procedure requires only five to ten minutes, no expensive equipment is required, trauma is minimized, the patient is not required to go to a laboratory (to which the biopsy specimen in 10 per cent formaldehyde is forwarded), and the method is more accurate and practical for the rural physician than is the use of a capillary tube and indirect dark field examination.

Chambers and Scholtz studied 104 genital lesions suspected of being chancres, 86 were proved to be syphilitic. Of these, the stain gave negative results in only 1, dark field examination in this case gave positive results. In the other 85 cases in which *S. pallida* was found in stained section, dark field examination was not done in 6, but in the remainder was positive in only 46 (58 per cent). The superiority of the staining method suggests its wider applicability, and it would be distinctly worth while for the laboratory of some state health department to determine its value relative to the already available capillary tube-dark field technic.

Involvement of Pelvic Nodes in Cervical Chancre—Hissard and Desmezerets¹¹¹ describe chancre of the cervix with satellite pelvic adenopathy as observed in 2 patients. De Gregorio and de Blasio,¹¹²

110 Chambers, S. O., and Scholtz, J. R. Clinical Application of Stain for Spirochetes (Krajan), *Arch. Dermat. & Syph.* **38**:217 (Aug.) 1938.

111 Hissard and Desmezerets, C. V. Chancres du col de l'utérus et adénopathie pelvienne, *Bull. Soc. franç. de dermat. et syph.* **45**:1731 (Nov.) 1938.

112 de Gregorio, E., and de Blasio, R. Sull'adenopatia pelvica satellite nella sifiloscrosi iniziale del collo dell'utero, *Rinasc. med.* **15**:619 (Sept. 30) 1938.

Simon¹¹³ and Delmas¹¹⁴ each report a similar condition and describe the method of palpation. The involved lymph node is located in the broad ligament. If the fingers are placed high in the lateral fornix of the vagina with the plantar surfaces facing laterally and are slowly and gently brought anteriorly, the node may be felt.

Osteitis in Patients with Early Syphilis—Osteitis and periostitis are rarely reported observed in patients with early syphilis. This is probably not because of the rarity of these conditions but mainly because patients with early syphilis who complain of headaches and pain in bones are not examined roentgenologically. Newman and Saunders¹¹⁵ describe osteolytic changes in the skull and both tibias of a patient with secondary syphilis. Squires and Weiner¹¹⁶ report, in a patient with secondary syphilis, several palpable small swellings of the skull, which on roentgen examination revealed circumscribed areas of decreased density. The reviewers can testify that destructive osteitis of the skull is not uncommonly found in patients with secondary syphilis if searched for.

Massive Doses of Arsenicals in the Therapy of Early Syphilis—It has long been pointed out that the standard methods of treatment of syphilis are unsatisfactory in that they are too uncertain in results, too painful and disagreeable, too dangerous, too time consuming and too expensive. These defects have led to an intensive search by many experimental chemotherapists for new and improved methods of preparing arsenic and the heavy metals, or for entirely new products unrelated to those now in use, but so far, though many new drugs have been produced which in one respect or another possess moderate advantages over earlier products, the search for a chemical which would fulfil Ehrlich's original idea of an immediate sterilizing cure of the disease has not been successful. On the whole, while chemotherapeutic research has lessened some of the disagreeable features of treatment and has minimized both its danger and its expense, it has neither improved greatly on the results obtainable with Ehrlich's original arsphenamine ("salvarsan") combined with mercury nor materially shortened the time essential for successful treatment. Nevertheless, this type of research is continuing and properly should continue.

113 Simon, C. Trois cas de chancres syphilitiques du col de l'utérus accompagnés d'adenopathie pelvienne satellite nettement perceptible au toucher vaginal, *Bull Soc franç de dermat et syph* **45** 604 (April) 1938.

114 Delmas, M. Chancre syphilitique du col utérin avec ganglion satellite pelvien accessible par voie vaginale, *Bull Soc franç de dermat et syph* **46** 713, 1939.

115 Newman, B. A., and Saunders, H. C. Skeletal System Manifestations During Secondary Syphilis, *New York State J Med* **38** 788 (May 15) 1938.

116 Squires, J. B., and Weiner, H. L. Osteitis in Early Syphilis. Report of a Case, *Arch Dermat & Syph* **39** 830 (May) 1939.

Chargin, Leifer and Hyman¹¹⁷ suggested in 1935 that early syphilis may be "cured" by a method of treatment which, though utilizing already available arsenical drugs (neoarsphenamine or mapharsen¹¹⁸), requires only five days for completion instead of the twelve to eighteen months necessary with the standard systems of treatment. The method involves the administration of large doses of the drug (with neoarsphenamine from five to six times, and with mapharsen from ten to fifteen times, the usual maximum therapeutic dose) given slowly by the continuous intravenous drip method over a five day period. It depends theoretically on the probable interrelationship between the concentration of the drug in the blood and tissue fluids and the spirocheticidal effect. When an arsenical drug is administered intravenously by the conventional divided dose technic its concentration in the blood rises momentarily to a very high level but promptly falls to much lower levels as the drug is removed from the circulation by the liver. With this standard method, a high concentration of the drug in the blood is probably not maintained for longer than an hour or two, thereafter the amount of therapeutically active drug in the body fluids is almost infinitesimal. To Chargin and his collaborators it seemed likely that a prolonged moderate concentration of the drug in the body might be more effective than a high concentration followed by a very much lower level, repeated at brief intervals.

This has been shown to be true of the administration of sulfanilamide and its derivatives for bacterial infections. There is a known critical concentration of sulfanilamide which must be maintained in the blood and tissues over a given period. If this concentration is too low, the bactericidal effect will not occur, if it is too briefly maintained, all the organisms will not have been destroyed, and relapse will follow.

In 1939 Hyman, Chargin and Leifer¹¹⁹ report further that, of the 25 patients originally treated by this method, 15 were available for a five year follow-up. The cerebrospinal fluid of 13 patients was examined and found normal. The serologic tests of 11 patients remained negative after forty-two months. One patient certainly and another probably had been reinfectd.

117 Chargin, L., Leifer, W., and Hyman, H. T. Studies of Velocity and the Response of Intravenous Injections. V. The Application of the Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis, *J. A. M. A.* **104** 878 (March 16) 1935.

118 The information as to mapharsen was obtained by personal communication with the authors.

119 Hyman, H. T., Chargin, L., and Leifer, W. Massive Dose Arsenotherapy of Syphilis by the Intravenous Drip Method. Five Year Observation, *Am. J. M. Sc.* **197** 480 (April) 1939.

Tzanck and collaborators¹²⁰ have published a number of papers on the massive dose method of treatment for syphilis (1.5 Gm of neoarsphenamine per day for three consecutive days, each dose being administered slowly, drop by drop, over a three to five hour period). Their work was not as well controlled as that of the group aforementioned. However, as nearly as can be determined from these very repetitive papers, about 170 patients (with early and with late syphilis) have been treated by this technic with satisfactory immediate results as to disappearance of surface spirochetes, healing of lesions and prompt serologic reversal. The follow-up, as stated, was wholly inadequate. There have been at least 2 deaths directly attributable to the treatment.

The results of Hyman and collaborators, and even those of Tzanck and his associates, suggest that what is true of sulfanilamide and bacterial infection may also be true of arsenic and syphilis. It is important to point out, however, that much further study is essential before the new method may be applied generally.

There are as yet inadequate data as to the toxicity of large doses of arsenical drugs given by this method. In human beings given neoarsphenamine in the arbitrarily selected dose of 4 to 5 Gm there was a high incidence of reactions, especially polyneuritis (35 per cent). It is desirable to redefine exactly in experimental animals the minimum lethal and the maximum tolerated dose with the new technic.

It is further desirable to redefine with the new method the minimum curative dose in experimental rabbit syphilis. With the usual single injection technic, the curative dose of arsphenamine is 10 to 12 mg per kilogram and that of neoarsphenamine is 15 to 25 mg per kilogram. The minimum curative dose of mapharsen is not definitely known, but it is certainly less than 6 mg per kilogram, perhaps as little as 2 to 3 mg per kilogram.

The clinical studies already carried out suggest that with the continuous intravenous drip method the minimum curative doses will be

120 Tzanck, A. Traitement arsenical massif de la syphilis (par instillation goutte a goutte). Son interet prophylactique, *Bull Acad de med*, Paris **119** 257 (March) 1938. Tzanck, A., Duperrat, R., and Lewi, S. Le traitement novarsenical massif par instillation intraveineuse goutte a goutte, *Bull et mem Soc med d hôp de Paris* **54** 268 (Feb 21) 1938, *Arsenotherapie massive intraveineuse par instillation goutte a goutte (technique)*, *J de med de Paris* **58** 341 (April 28) 1938. Tzanck, A., Pautrat, J., and Moline, R. Arsénotherapie massive par instillation veineuse goutte a goutte, *ibid* **58** 283 (April 7) 1938. Tzanck, A. Syndrome secondaire mortel apres traitement arsenical massif, *Bull Soc franç de dermat et syph* **45** 487 (April) 1938, *Le traitement massif arsenical de la syphilis*, *Bruxelles-med* **18** 1642 (Oct 30) 1938. Loeper, M., Tzanck, A., and Brouet-Santon, J. Un cas de mort par surrenalite hemorrhagique, apres injections massives de norvaisenobenzol, *Bull et mem Soc med d hôp de Paris* **54** 767 (May 16) 1938.

found to be much smaller. From the standpoint of toxicity, moreover, it is important to determine experimentally not only that animals will survive the injection of the minimum curative dose but also, by necropsy of animals so treated at varying intervals thereafter, that permanent damage to important tissues is lacking.

Since the clinical studies suggest that a curative effect depends on moderate prolonged concentration of the spirocheticidal substance in the blood, it is clear that this in turn depends on the interrelationship of dosage and time of administration. Observations on syphilis in experimental animals, while not directly transferable to syphilis in man, will nevertheless permit a more exact definition of these relationships. Such observations may show that comparable clinical results may be accomplished in a still shorter time than the apparently arbitrarily chosen five days or with a smaller and therefore perhaps safer dose than any so far arbitrarily selected.

The all important time-dose relationship should be checked not only by studies in experimental animals but also by chemical studies of excretion (already in progress) and of the concentration of the curative drug in the blood and tissues of the patient.

Nothing is known as yet of the possible effects of this method of treatment in various forms of late syphilis. It is generally thought that one reason for the less satisfactory curative results (in the biologic sense) of treatment in late as compared with that in early syphilis lies in the fact that in the late stages of the disease the organisms tend to localize in tissues which the relatively poorly diffusible trivalent arsenical drugs fail to reach in spirocheticidal concentration.

This consideration, together with the fact that in bacterial infections sulfanilamide and its derivatives owe much of their success to their extremely rapid diffusibility to all tissues of the body, suggests that the trivalent arsphenamines, which are semicolloids possessing relatively poor penetrability for tissues, presumably because they combine with serum proteins to form complexes which are either inactive or nondiffusible or both, may be much less suitable for this method of treatment than the arsenoxides, which probably do not so combine and which are therefore theoretically more readily diffusible. Indeed, it is still further suggested that other drugs much less effective than either the arsphenamines or the arsenoxides when administered by the conventional technic may prove to be superior by the new method because of the factor of greater diffusibility.

As yet, therefore, not only are the factors of dosage and proper duration of treatment unsettled, but it is not yet certain that the most suitable drug or group of drugs for this particular technic has been found.

From the immediate practical standpoint, finally, it must be emphasized that the method is one which necessitates at least one week of full hospitalization, that its dangers have not yet been accurately defined and that the patients so far reported on have been followed for an interval too short to determine the permanency of results

While the method is therefore still in the experimental stage and unsuitable for mass application, it may nevertheless prove to be of major importance both to the individual patient and to the public. Further intensive study is amply justified

TRANSFUSION SYPHILIS

DeBakey and Honold¹²¹ reemphasize the fact that syphilis is often transmitted during transfusion of blood because of lack of precautions in the selection of a donor. Frequently syphilis is so transmitted from a relative or a friend. An analysis of the reported cases of transfusion syphilis shows that the infection was usually transmitted when the donor was in the early stage of the disease, occasionally when the result of his serologic test for syphilis was negative. This view is upheld by McCluskie,¹²² who reports 3 cases in which syphilis was transmitted in transfusion from donors who were clinically and serologically without evidence of such infection at the time of transfusion. All 3 of these persons presented primary lesions and positive serologic reactions shortly after serving as donors. McCluskie suggests that the risk of transfusion syphilis could be minimized by the use of blood from cadavers or, better still, by some means of rapidly destroying spirochetes in the blood withdrawn from the donor.

Such a method of destroying spirochetes in the donor's blood has recently been proposed by Kast, Peterson and Kolmer,¹²³ who, confirming Eagle's work as to the spirocheticidal activity of arsphenamine and neoarsphenamine in vitro, suggest the use of either drug in citrated blood to be used for transfusions. They seeded citrated blood with virulent *S. pallida*, added neoarsphenamine or arsphenamine in a final dilution of 1:20,480 and allowed the mixture to remain at room temperature for fifteen minutes. Such blood when injected into nonsyphilitic rabbits did not produce syphilis, though control animals inoculated with blood plus organisms but minus the arsphenamine become infected. The

121 DeBakey, M., and Honold, E. Blood Transfusion. Indications, Contraindications and Complications, *Internat. M. Digest* **33** 301 (Nov.) 1938

122 McCluskie, J. A. W. The Transmission of Syphilis by Blood Transfusion, *Brit. M. J.* **1** 264 (Feb. 11) 1939

123 Kast, C. C., Peterson, C. W., and Kolmer, J. A. The Treponemicidal Activity of Arsphenamine and Neoarsphenamine in Vitro with Special Reference to Citrated Blood and Suggested Method for the Prevention of Transfusion Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **23** 150 (March) 1939

suggested dilution of neoarsphenamine or arsphenamine is not toxic to the recipient

LATE SYPHILIS

General Considerations—Hasselmann¹²⁴ discusses syphilis in Arabs living between the Mediterranean Sea and the Persian Gulf. He believes that, because of racial, climatic and nutritional conditions, syphilis may manifest itself in different forms. The diseases known by various colloquial terms, such as "firjal" and "latta" in parts of Palestine, "loath" and "bejel" in the region of the Euphrates and the Tigris River valleys (Iraq and Syria), "laghout" in Lebanon, and "abou-laghif" and "jaifór" in Trans-Jordan, are, he thinks, all syphilis. Butler¹²⁵ attempts unsuccessfully to show that syphilis, yaws and bejel are one and the same disease.

Syphilis of the Stomach—Carey and Ylvisaker¹²⁶ suggest that a gastroscopic examination may aid in the diagnosis of syphilis of the stomach. They review the brief literature on the subject and report on a patient whom they observed and whose stomach they examined by gastroscope. The common feature is the small gastric lumen, particularly at the antrum. The normal gastric folds are effaced, and the mucosa is atrophic. The mucosal surface is granular, and superficial ulcerations may be present. Little air can be introduced into the stomach. In their patient the stomach after antisyphilitic treatment returned to its normal appearance.

Davicovic¹²⁷ also reports on a patient with syphilis whose stomach was examined by gastroscope. There was observed diffuse thickening of the mucous membrane in the anterior pyloric region with numerous small ulcerations in this area.

Paroxysmal Hemoglobinuria—Dill¹²⁸ reinvestigated latent paroxysmal hemoglobinuria. Donath-Landsteiner tests were done on 360 syphilitic patients and 160 nonsyphilitic patients who were used as controls. Latent paroxysmal hemoglobinuria as indicated by the Donath-Landsteiner test occurred only once in the 360 syphilitic patients and

124 Hasselmann, C. M. Syphilis Among Arabs in the Near East. Bejel and Loath in Iraq and Syria, Firjal and Latta in Palestine, Laghout in Lebanon, Abou-Laghif and Jaifor in Trans-Jordan, *Arch Dermat & Syph* **38** 837 (Dec) 1938.

125 Butler, C. S. The Septic Syphilodermata, *Am J Clin Path* **9** 1 (Jan) 1939.

126 Carey, J. B., and Ylvisaker, R. S. Gastroscopic Observations of Syphilis of the Stomach, *Ann Int Med* **12** 544 (Oct) 1938.

127 Davicovic, S. La syphilis gastrique, *Presse méd* **47** 275 (Feb 18) 1939.

128 Dill, L. V. Observation on the Incidence of Latent Paroxysmal Hemoglobinuria as Evidenced by the Donath-Landsteiner Phenomenon, *Am J Syph, Gonorr & Ven Dis* **23** 220 (March) 1939.

not at all in the control group. The author states that, according to the literature, the incidence of latent paroxysmal hemoglobinuria has ranged from 5 to 30 per cent. In his own series the incidence was 0.025 per cent. The discrepancy, he feels, may be due to the more intensive anti-syphilitic treatment now employed or to a difference in the clinical material studied.

Juxta-Articular Nodules—In a detailed discussion of rheumatic subcutaneous nodules and lesions simulating them, Keil¹²⁹ points out that syphilitic juxta-articular nodules are uncommon and that many of those which occur do so as a solitary manifestation of late syphilis. There is a striking similarity of these nodules to those of rheumatic fever. They are most commonly found at the elbow, knee and hip and less commonly at the ankle, shoulder and sacrum. They are as a rule symmetrically placed, are about the size of a walnut or smaller, develop slowly and may be soft at first but with increasing age become harder. They respond to antisyphilitic therapy, disappearing in a few weeks. With ordinary staining methods there is no characteristic pathologic change in the nodules diagnostic of syphilis. The diagnosis of syphilitic juxta-articular nodule rests on (1) the association with other manifestations of syphilis, (2) the almost invariable presence of a positive serologic test for syphilis and (3) the striking response to antisyphilitic treatment.

CARDIOVASCULAR SYPHILIS

Incidence—Welty¹³⁰ has analyzed the incidence of cardiovascular syphilis in 15,000 consecutive cases in which necropsy was performed between 1927 and 1937. Cardiovascular syphilis was observed in 1,040 cases (6.93 per cent). In 192 of these the condition was aneurysm, in 216, aortic insufficiency, and in the remaining 632, simple aortitis. Seventy-four per cent of all patients were males. Sixty-eight per cent of all patients were Negroes. To demonstrate the decreasing incidence of cardiovascular syphilis over this ten year period, Welty divides his material into five groups of 3,000 autopsies each. Each group represents a period of eighteen to thirty months.

Thompson, Comeau and White¹³¹ studied 241 patients from the standpoint of the effect of adequate and of inadequate treatment for early syphilis on the subsequent development of cardiovascular syphilis. All patients in the group had had syphilis for fifteen to twenty-five

129 Keil, H. The Rheumatic Subcutaneous Nodules and Simulating Lesions, *Medicine* **17** 261 (Sept.) 1938.

130 Welty, J. W. A Necropsy Survey of Cardiovascular Syphilis with Particular Reference to Its Decreasing Incidence, *Am J M Sc* **197** 782 (June) 1939.

131 Thompson, W. P., Comeau, W. J., and White, P. D. The Role of the Treatment of Syphilis in the Prevention of Cardiovascular Involvement, *Am Heart J* **17** 286 (March) 1939.

years Eighteen patients (7 per cent) had definite cardiovascular syphilis and 8 (3 per cent) probable aortitis No cardiovascular abnormalities were discovered in 190 subjects, while 25 (10 per cent) had questionable dilatation of the aorta The patients were divided into three groups according to the amount of treatment received for early syphilis 172 (71 per cent) had received less than twelve injection of an arsenical with equivalent heavy metal, 33 (14 per cent) had received thirteen to nineteen injections of an arsenical with equivalent heavy metal, and 36 patients (15 per cent) had received more than twenty doses of an arsenical with equivalent heavy metal Of the 18 patients with definite cardiovascular syphilis, 17 fell into the first treatment group and 1 into the second The authors conclude that their study supports the clinical impression that adequate treatment of early syphilis tends to prevent later clinical manifestations of cardiovascular syphilis Blair,¹³² in a general

1927 to 1930	276 cases		92 per 1000
			1 per 11 deaths
1930 to 1932	231 cases		77 per 1000
			1 per 13 deaths
1932 to 1934	191 cases		63.6 per 1000
			1 per 16 deaths
1934 to 1935	174 cases		58 per 1000
			1 per 17 deaths
1935 to 1937	168 cases		56 per 1000
			1 per 18 deaths

Fig 3—Decreasing incidence of cardiovascular syphilis at the Philadelphia General Hospital (after Welty¹³⁰)

discussion of cardiovascular syphilis, remarks that almost none of such patients seen in his clinic has had adequate previous treatment and that a large percentage have had none

Gumma of the Heart—Diffuse gummatous myocarditis is rare Von Haam and Ogden¹³³ stated that only 7 cases had been reported between 1845 and 1935 They studied the protocols of 5,213 autopsies and found that gummatous lesions of the heart had been demonstrated only in 3—in the first, isolated gummatous pericarditis, in the second, multiple gummatous myocarditis, and in the third, diffuse gummatous myocarditis and syphilitic endocarditis

¹³² Blair, A Early Recognition of Cardiovascular Syphilis, New York State J Med **38** 1115 (Aug 15) 1938

¹³³ Von Haam, E, and Ogden, M A Syphilis of the Heart and Pericardium, Arch Path **26** 525 (Aug) 1938

Two cases of the relatively uncommon gumma of the interventricular septum are reported, one by Cossio, Vivoli and Caul¹³⁴ (remarkable for the previously unreported association of ventricular tachycardia) and the other by Coelho and d'Oliveira,¹³⁵ in which both ventricular tachycardia and ventricular fibrillation were observed

Aortitis—Herzog¹³⁶ believes the diagnosis of syphilitic aortitis may be facilitated by taking the blood pressure in both arms simultaneously. Two blood pressure cuffs are connected with a manometer by means of a Y tube. By using a sphygmophone, with one ear piece connected to the tubing leading to each arm, the exact time of the appearance of the beats can be determined. The blood pressure of normal persons and of those with essential hypertension are said usually to be equal in both arms. In syphilitic aortitis the pressures are often unequal.

Epstein¹³⁷ describes a method by which the aorta can be more clearly visualized on the roentgen film. The method is overpenetration, which enables one to outline regions more closely where structures are superimposed.

Aneurysm—Two very interesting statistical studies of aneurysm are presented by Mills and Horton¹³⁸ and by Kampmeier.¹³⁹ Mills and Horton, working at the Mayo Clinic, analyze the observations on 596 patients with aneurysm observed in the years 1925 to 1935, inclusive, especially those relating to location of the aneurysm and the etiologic role of syphilis. The results are shown in the table. Practically all except 6 of the patients were white persons. Syphilis is rarely, if ever, a cause of intracranial aneurysm, which is usually due to embolism, congenital defect or arteriosclerosis. Likewise it is rarely the responsible factor in aneurysm of the abdominal aorta or of vessels of the extremities. Most physicians believe, however, that the presence of a thoracic aneurysm is tantamount to a diagnosis of syphilis. It is of great interest therefore that Mills and Horton could obtain no history of

134 Cossio, P., Vivoli, D., and Caul, H. Syphilis of the Interventricular Septum and Ventricular Tachycardia, *Am J M Sc* **194** 369 (Sept.) 1937

135 Coelho, E., and d'Oliveira, A. Syphilis de la cloison intraventriculaire et tachycardie ventriculaire. syphilis de l'artere pulmonaire (pulmonarterite syphilitique), *Arch d mal du cœur* **32** 17 (Jan.) 1939

136 Herzog, F. Simultaneous Bilateral Measurement of Blood Pressure for Diagnosis of Syphilitic Aortitis, *Orvos hetil* **82** 747 (July 30) 1938

137 Epstein, S. H. The Visualization of the Aorta by the Method of Roentgenographic Overpenetration, *Am J Roentgenol* **40** 396 (Sept.) 1938

138 Mills, J. H., and Horton, B. T. Clinical Aspects of Aneurysm, *Arch Int Med* **62** 949 (Dec.) 1938

139 Kampmeier, R. H. Saccular Aneurysm of the Thoracic Aorta. A Clinical Study of Six Hundred and Thirty-Three Cases, *Ann Int Med* **12** 624 (Nov.) 1938

syphilis, nor any physical or laboratory evidence of the disease, from 30 per cent of the 339 patients studied. Only 35 necropsies were performed in the series with thoracic aneurysm, and the authors provide no data as to postmortem evidence of syphilis. The average duration of life after the diagnosis of thoracic aneurysm was established was twenty and one-half months, but the authors did not relate this datum to the presence or absence of antisyphilitic treatment.

Kampmeier's paper deals exclusively with saccular aneurysm of the thoracic aorta. Of 1,113 cases data on which were available for analysis from the Charity Hospital of New Orleans and the Vanderbilt University Hospital, 633 were acceptable for study. The incidence of the clinical diagnosis of thoracic aneurysm in many large hospitals of the world is probably about 1 in 1,000 medical admissions, that of the post-mortem diagnosis is probably about 1 in 100. This suggests that during life the condition is much more often missed than diagnosed. In Kamp-

*Location of Aneurysm and Incidence of Syphilis,
According to Mills and Horton¹³⁸*

Location of Aneurysm	Cases		Percent Incidence of Syphilis
	Number	Percentage	
Intracranial	143	24	3.5
Thoracic	339	56.9	70.0
Abdominal	80	13.4	8.8
Extremities	21	3.5	9.5
Miscellaneous	13	2.2	7.7
Total	596	100.0	

meier's personal material the ratio of aneurysms to admissions was about the same for the years 1906 to 1930, but in the period 1931 to 1935, inclusive, the frequency of aneurysm decreased by more than half, suggesting that modern treatment is finally beginning to exert a preventive effect.

Kampmeier presents a more complete analysis of his cases for syphilis than do Mills and Horton. In only 289 of the 467 cases in which tests for syphilis were made were the tests positive (62 per cent), but when to this figure are added the cases in which there was a definite history of previous syphilis or of treatment for it, or other clinical, laboratory or necropsy evidence of syphilis, the incidence of syphilis rises to 81 to 84 per cent. While he does not definitely say so, Kampmeier evidently feels that the percentage of cases in which syphilis was a cause of thoracic aneurysm would have been even higher if the patients had been more carefully studied.

There is a careful analysis of the material by race, sex, age, occupation, anatomic classification, chief complaint, symptoms, physical signs,

roentgenologic evidence, cause of death, prognosis and differential diagnosis. The cause of death was definitely known in 247 cases. Death was due to rupture in 39 per cent, to respiratory obstruction in 18 per cent, to cardiac failure in 11.5 per cent, to pneumonia in 9 per cent and to scattering causes or causes unknown in the remainder.

The duration of life from the onset of symptoms to death was known in 224 cases, and was known to be three years or longer in only 18 of these. The average life expectancy was only six and four-tenths months. Unfortunately, however, Kampmeier does not relate these data to the presence or absence of treatment. It will be recalled that Padget and Moore¹⁴⁰ have shown that even with inadequate antisyphilitic treatment the duration of life in patients with aneurysm is prolonged to an average of thirty-two months, and in well treated patients, to an average of fifty-five months, after the development of symptoms.

Shimkin¹⁴¹ collects from the literature 44 cases in which aortic aneurysm caused compression of the spinal cord, and adds 2 of his own.

Maurer¹⁴² brings to attention that complete absence of pulsation in the radial, brachial and carotid arteries is rare. Five cases have been reported previously in which this was associated with aneurysm of the aortic arch, to these Maurer adds 2 cases in which this association was noted at necropsy at the Cincinnati General Hospital. The presenting complaint in all cases was referable to the cerebrum, evidently caused by cerebral anoxemia.

Armstrong, Coggin and Hendrickson¹⁴³ assemble 98 reported cases of spontaneous arteriovenous aneurysm of the thorax to which they add 2 cases. Prior to 1925 syphilis was mentioned as the cause of the condition in less than half of the reported cases, though since 1925 syphilis has been thought to be the cause in 77 per cent of the 26 cases described. Symptoms and signs could be analyzed in 80 cases. All patients had cyanosis, and 79 had swelling about the upper part of the thorax. The onset was sudden in 50 patients. Dyspnea on exertion was shown in 35, and 9 had orthopnea. Unconsciousness was reported in 11, severe pain in 15 and difficulty in swallowing in 6. A majority had signs of a tumor in the thorax. Occasionally a suprasternal thrill was palpable. Abnormal cardiac sounds were noted in 77 of the 80 patients, in 30 the

140 Padget, P., and Moore, J. E. The Results of Treatment in Cardiovascular Syphilis, *Am Heart J* **10** 1017 (Dec.) 1935.

141 Shimkin, M. B. Aneurysm of the Aorta with Compression of the Spinal Cord. Two Case Reports and Review of the Literature, *Ann Int Med* **12** 1709 (April) 1939.

142 Maurer, E. Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch, *Am Heart J* **17** 716 (June) 1939.

143 Armstrong, E. L., Coggin, C. B., and Hendrickson, H. S. Spontaneous Arteriovenous Aneurysms of the Thorax. A Review of the Literature with a Report of Two Cases, *Arch Int Med* **63** 298 (Feb.) 1939.

machinery murmur of arteriovenous aneurysm was heard, in 22 there was a definite to and fro murmur. Death occurred in 54 of the 80 patients in less than one month after the onset of symptoms. Three died instantaneously. Collateral circulation was established in only 3 of the 81 patients.

Penick¹⁴⁴ discusses various operative methods for wiring aortic aneurysms.

Thyrotoxicosis and Syphilitic Heart Disease—Among 5,000 cases of heart disease, Maher and Plice¹⁴⁵ found 12 cases in which syphilitic heart disease was coexistent with thyrotoxicosis. Maher and Wosika¹⁴⁶ have studied these 12 cases to determine what effect one condition might have on the other. In 9 of the 12 cases the thyriopathy was classified as toxic adenoma and in 3 as exophthalmic goiter. Syphilitic infection antedated the development of goiter in every case. Histologic examination of the removed glands showed no evidence of syphilis. Contrary to the authors' expectation, their patients tolerated thyroidectomy remarkably well. No deaths followed operation, in spite of aortic insufficiency in 3 patients and aortic insufficiency and aneurysm in a fourth. The additional burden of thyrotoxicosis in syphilitic heart disease seemed to precipitate auricular fibrillation and congestive failure. Cure of the thyrotoxicosis relieved this burden on the heart and allowed it to return to normal rhythm and compensation. Those patients who were given antisymphilitic treatment before operation showed no cardiac improvement. Auricular fibrillation and congestive failure were uninfluenced. On the contrary, those patients who were operated on immediately showed marked improvement and no mortality.

Effect of Warm and Cold Weather—Bean and Mills¹⁴⁷ find that coronary occlusion and congestive heart failure from arteriosclerotic and rheumatic heart disease are more common during the winter months, but that there is no such seasonal variation in congestive heart failure due to syphilitic aortic regurgitation. They believe this discrepancy to be due to the rapid progression of cardiovascular syphilis.

144 Penick, R. M., Jr. Technic for Wiring Aortic Aneurysms, *South M. J.* **31** 1096 (Oct.) 1938.

145 Maher, C. C., and Plice, S. G. Multiple Etiological Factors in Five Thousand Cases of Heart Disease in Chicago, *Am. Heart J.* **14** 490 (Oct.) 1937.

146 Maher, C. C., and Wosika, P. H. The Combination of Thyrotoxicosis and Syphilitic Heart Disease, *Urol. & Cutan. Rev.* **43** 34 (Jan.) 1939.

147 Bean, W. B., and Mills, C. A. Coronary Occlusion, Heart Failure and Environmental Temperatures, *Am. Heart J.* **16** 701 (Dec.) 1938. Mills, C. A., and Bean, W. B. The Timing of Luetic Heart Failure in Relation to Heart Load, *Urol. & Cutan. Rev.* **43** 32 (Jan.) 1939.

NEUROSYPHILIS

Argyll Robertson Pupil—Costello¹⁴⁸ presents a review of the literature on Adie's syndrome. He reports 2 cases and calls attention to the difficulty of differentiating the Argyll Robertson pupil of neurosyphilis from the tonic pupil of Adie's syndrome.

Atrophy of the Optic Nerve—There will shortly appear jointly in the January 1940 numbers of the *American Journal of Ophthalmology* and the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* an exhaustive review of the pathogenesis and pathologic appearance of syphilitic primary atrophy of the optic nerve¹⁴⁹. This review will be followed (in the *American Journal of Ophthalmology* only) by a second review dealing with more general considerations of primary atrophy of the optic nerve and its treatment¹⁵⁰. These two reviews include the literature on the subject from 1932 to the present in much greater detail than is permissible here. Reference to recent articles on atrophy of the optic nerve will therefore be omitted from this review.

Constitutional Factors in Neurosyphilis—Stegmann¹⁵¹ has studied from a psychiatric standpoint the family histories of 270 patients with dementia paralytica. He reports a much higher incidence of psychoses in the relatives of these patients than in those of average normal persons and believes that the majority of such patients show some evidence of mental abnormality even before infection with syphilis.

The same point is covered for tabes dorsalis by Curtius, Schlotter and Scholz,¹⁵² who present monographically their conclusions as to this and other constitutional factors. Their study of 101 patients with this condition is of little value to the clinician. Of the 262 pages of text, 160 are devoted to a survey of constitutional and individual and familial predisposing factors and 38 to the effect of service on the development of tabes dorsalis. Only 39 pages are given to clinical considerations, and

148 Costello, M. J. A Syndrome Simulating Tabes Dorsalis, New York State J. Med. **39** 781 (April 15) 1939.

149 Moore, J. E., and Woods, A. C. The Pathology and Pathogenesis of Syphilitic Primary Optic Atrophy. A Critical Review, Am J Ophth., January 1940, to be published, Am J Syph., Gonorr. & Ven. Dis., January 1940, to be published.

150 Moore, J. E., and Woods, A. C. Syphilitic Primary Optic Atrophy. General Considerations and the Results of Treatment by Standard Methods (Especially Subdural Treatment and Induced Fever), a Critical Review, Am J Ophth., 1940, to be published.

151 Stegmann, A. Disposition und Belastung zur progressiven Paralyse, Allg. Ztschr. f. Psychiat. **108** 115, 1938.

152 Curtius, F., Schlotter, H., and Scholz, E. Tabes dorsalis. Klinische, erb- und konstitutionspathologische sowie sozialmedizinische Untersuchungen, unter Verwertung der Erfahrungen aus der Kriegsbeschädigten-Versorgung, in Martineck. Arbeit und Gesundheit. Sozialmedizinische Schriftenreihe aus dem Gebiete des Reichsarbeitsministeriums, Leipzig, Georg Thieme, 1938, no. 33.

no space is allotted to treatment. On the whole, the monograph might more profitably have been presented as a series of short papers in the periodical literature. The conclusions of the authors, based on an elaborate presentation of individual case histories, tables and charts, are that the various factors of human constitution which they studied play no role in the pathogenesis of tabes dorsalis, except bodily habitus, which is frequently of the asthenic type (though they fail to make it clear whether tabes develops in patients because they are asthenic or the asthenic habitus develops because of tabes), and "neuropathic constitution." By the latter term they mean that the families of tabetic patients include a higher proportion of psychiatrically unstable persons than do those of normal people. Many constitutional factors are considered in great detail, and though the results are largely negative, the work will be of value to students of this phase of medicine.

Bladder in Neurosyphilis—In previous reviews (1935 to 1938, inclusive) there has been included comparatively little discussion of the newer methods of study of the bladder in neurosyphilis, the only references provided being to articles by Langworthy and his associates¹⁵³ in the reviews of 1936 and 1937, to Rubritius¹⁵⁴ and Muschet¹⁵⁵ in the review of 1937 and to Palmer and Gernon¹⁵⁶ and Levin¹⁵⁷ in that of 1938.

The subject is, however, of such increasing importance in the diagnosis and management of neurosyphilis that a more complete bibliography covering the period of these reviews is fully justified and is herewith provided¹⁵⁸. The technical urologic procedure of cystometry,

153 Dees, J. E., and Langworthy, O. R. Experimental Study of Bladder Disturbances Analogous to Those of Tabes Dorsalis, *J. Urol.* **34**:359 (Nov.) 1935. Langworthy, O. R., Lewis, L. G., Dees, J. E., and Hesser, F. H. Clinical Study of the Control of the Bladder by the Central Nervous System, *Bull. Johns Hopkins Hosp.* **58**:89 (Feb.) 1936. Langworthy, O. R., Dees, J. E., and Lewis, L. G. Abnormalities of Micturition Due to Syphilis of the Nervous System, *Am. J. Syph., Gonorr. & Ven. Dis.* **20**:364 (July) 1936.

154 Rubritius, H. Die Miktionsstörungen der Tabiker, *Wien klin. Wchnschr.* **50**:311 (March 5) 1937.

155 Muschet, M. Cystometric Studies. The Value of Follow-Up Examinations, *Am. J. M. Sc.* **192**:693 (Nov.) 1936.

156 Palmer, E., and Gernon, J. T. The Use of Ergotamine Tartrate in the Treatment of the Tabetic Bladder, *Illinois M. J.* **72**:77 (July) 1937.

157 Levin, P. M. Action of Acetyl-Beta-Methylcholine Chloride (Mecholyl) in Neurologic Disturbances of the Urinary Bladder, with a Note on the Mechanism of Spinal Shock, *J. Pharmacol. & Exper. Therap.* **62**:449 (April) 1938.

158 Adson, A. W. Value of Sympathectomy in Treatment of Cord Bladder, *Northwest Med.* **33**:276 (Aug.) 1934. von Noszkay, A. Zur Frage der chirurgischen Behandlung von Blasen mit verminderter Fasskraft (Kapazität) (Prasakrale Sympathikusresektion, Harnleiterverlagerung), *Ztschr. f. Urol.* **28**:829, 1934. Watkins, K. H. Clinical Value of Bladder Pressure Estimation,

introduced a decade or more ago, has been further studied by application not only to patients with various neurologic diseases but also to experimental animals in which various types of lesions of the spinal cord have been produced. The Baltimore group of investigators headed by Langworthy (a neurologist) and Lewis (a urologist) has been especially interested. While much remains to be done, a number of points of practical interest appear. An abnormal cystometrogram may be the earliest sign of injury to the cord in neurosyphilis, obtainable before the development of any but very minor urinary symptoms and before other objective evidence of neurologic damage can be demonstrated.

Brit J Urol **6** 104 (June) 1934 Creevy, C D Neurogenic Dysfunction of the Bladder, Alterations in Physiology of Micturition Due to Lesions of the Nervous System, Arch Neurol & Psychiat **34** 777 (Oct) 1935 Deakin, R Clinical Demonstration (in Case of Tabetic Bladder) and Effect of Mecholyl (Acetyl-Beta-Methyl-Choline-Chloride), Urol & Cutan Rev **39** 110 (Feb) 1935 Fulcher, O H Presacral (Superior Hypogastric Plexus) Neurectomy for Certain Vesical Conditions (with Especial Reference to Cord Bladder), West Virginia M J **31** 465 (Oct) 1935 Gernon, J T, Ewert, E E, and Herrold, R D Use of Acetylbetamethylcholine Chloride in Treatment of Neurogenic Bladder and Allied Conditions Preliminary Report, M Rec **141** 141 (Feb 6) 1935 Goyanes, J, Jr Tratamiento quirurgico de la disfuncion neurogenica vesical, de la enfermedad de Hirschsprung y de la dismenorrea por simpaticectomia lumbar y presacral (plexo de Hovelacque), Arch de med, cir y especialid **38** 837 (Dec 30) 1935 Horn, K W Mecholin (Acetyl-Beta-Methylcholine-Hydrochloride) in the Treatment of Certain Types of Atonic Bladder, Univ Hosp Bull, Ann Arbor **1** 3 (March) 1935 Lewis, L G, Langworthy, O R, and Dees, J E Bladder Abnormalities Due to Injury in Motor Pathways in Nervous System, J A M A **105** 2126 (Dec 28) 1935 McCaughan, J M, and Hershey, J H Diagnosis of Neurogenic Lesions by Cystometry Appraisal of Method Based on Experimentation with Animals, Arch Surg **30** 956 (June) 1935 Rose, D K Cystometry, Urol & Cutan Rev **39** 107 (Feb) 1935 Creevy, C D Treatment of Overflow of Neurogenic Vesical Dysfunction, J Urol **35** 507 (May) 1936, Minnesota Med **19** 269 (May) 1936 Forssmann, W Harnverhaltung und Harnsperre, Med Klin **32** 1262 (Sept 11) 1936 Gernon, J T, Palmer, E, and McKenna, C M Recent Developments in Treatment of Neurogenic Dysfunction, Based on Cystometry, J Urol **35** 515 (May) 1936 Grant, F C Surgery of Autonomic System of Urinary Tract (Section of Presacral Nerve or Superior Hypogastric Plexus), *ibid* **36** 618 (June) 1936 Langworthy, O R New Approach to Diagnosis and Treatment of Disorders of Micturition in Diseases of Nervous System, Internat Clin **3** 98 (Sept) 1936 Lewis, L G, and Dees, J E Diagnosis and Treatment of Neurologic Bladder, S Clin North America **16** 1257 (Oct) 1936 Muschet, M Diagnosis of Neurogenic Bladder by Means of Cystometer, Pennsylvania M J **39** 493 (April) 1936 Rose, D K Present Status of Cystometry, J A M A **107** 1534 (Nov 7) 1936 Brodie, E L, and Phifer, I A Cystometric Observations in Asymptomatic Neurosyphilis Preliminary Report, J Urol **38** 419 (Oct) 1937 Cheetham, J G Presacral Neurectomy (Resection of Superior Hypogastric Plexus) for Relief of Certain Types of Bladder Dysfunction, *ibid* **37** 148 (Jan)

The interpretation of cystometric abnormalities when neurosyphilis is otherwise asymptomatic is as yet difficult because of the fact that similar abnormalities may sometimes be found in studies of apparently healthy persons (Boyd and Smith ¹⁵⁹)

Since symptoms of disturbance of the bladder are, as is well known, often among the earliest signs of tabes dorsalis, a definite prognostic statement that this neurologic disease is imminently developing may sometimes be made by urologic consultation, including cystometry. Moreover, it is possible, by this procedure, to differentiate between damage to the posterior columns of the spinal cord, as in tabes, and lesions of the corticospinal tracts, as in other forms of neurosyphilis.

1937 Creevy, C D Treatment of Neurogenic Vesical Dysfunction Complicated by Lesions of Vesical Outlet, *ibid* **37** 593 (April) 1937 Hortolomei, N, and Streja, M De l'utilité de la cystométrie, *J belge d'urol* **10** 531 (Dec) 1937 Muschet, M, Carp, J, and Charny, C W Normal Cystometrogram, *J Urol* **37** 718 (May) 1937 Simeone, F A, and Lampson, R S Cystometric Study of Function of Urinary Bladder, *Ann Surg* **106** 413 (Sept) 1937 Simons, I Cystometry Studies in Bladder Function, Critical Review with Special Reference to Microcystometry and Sphincterometry, *Brit J Urol* **9** 132 (June) 1937 Van Duzen, R E Neurogenic Disturbances of Bladder Function, *J Urol* **37** 156 (Jan) 1937 Adams, P S Use of Cystometer in Diagnosis of Neurogenic Bladders (with Comments on Treatment and Case Reports), *Nebraska M J* **23** (Feb) 1932 Boyd, M L, and Smith, W A Why Are Abnormal Cystometrograms Obtained in Normal Patients? *J Urol* **40** 513 (Oct) 1938 Cheetham, J G Clinical Evaluation of Cystometer, *ibid* **39** 569 (April) 1938 Gill, R D Neurogenic Disturbances of Bladder Physiology, Pathology, Symptomatology and Diagnosis, *ibid* **40** 797 (Dec) 1938 Herbst, W P Treatment of Neurogenic Diseases of Bladder, *ibid* **40** 789 (Dec) 1938 Heusser, H Die Manometrie der Harnblase (Cystometrie), *Ztschr f urol Chir u Gynak* **44** 312, 1938 Irazu, J Cistometría (nota previa), *Rev argent de urol* **7** 283 (Sept-Oct) 1938 Kasztriner, I, and Illyes, E Urologic Diseases of Neurologic and Psychogenic Origin with Special Consideration of Tabetic Vesical Disorders, *Gyógyászat* **78** 135 (Feb 27), 162 (March 6), 174 (March 13) 1938 Lewis, L G, and Langworthy, O Cystometry, *J Urol* **40** 677 (Nov) 1938 Magid, M A Value of Cystometric Studies in Atonic Bladder, *Rocky Mountain M J* **35** 299 (April) 1938 Maitland, A I L Dysfunction of Bladder as Early Neurologic Symptom, *Tr Roy Med-Chir Soc Glasgow*, 1937-1938, p 145, in *Glasgow M J*, June 1938 McLellan, F C Neurogenic Bladder Preliminary Report, *Univ Hosp Bull*, *Ann Arbor* **4** 43 (June) 1938 Povlsen, O Cystometry, *Hospitaltid supp*, *Festskr Bisp Hosp* **81** 137, 1938 Simons, I Cystometry Status and Outlook, with Special Reference to Microcystometry and Sphincterometry, *Urol & Cutan Rev* **42** 316 (May) 1938, *Neurologic Studies by Means of Microcystometer and Sphincterometer Studies in Bladder Function (Preliminary Report)*, *J Urol* **39** 791 (June) 1938 Brodie, E L, Helfert, I, and Phifer, I A Cystometric Observations in Neurosyphilis, *Urol & Cutan Rev* **43** 51 (Jan) 1939 Rose, D K, and Shefta, L M Tabetic Bladder Discussion of Etiology with Cystometric and Pathologic Study, *South M J* **32** 549 (May) 1939

159 Boyd, M L, and Smith, W A Why Are Abnormal Cystometrograms Obtained in Normal Patients? *J Urol* **40** 513 (Oct) 1938

Particularly important is the fact that by this technic a competent urologist is often able to define clearly to what extent urinary symptoms in a neurosyphilitic patient are due to partial obstruction or to damage to the innervation of the musculature of the bladder

Finally, cystometry is of value in determining the proper method of treatment, e g, whether one should employ acetylbetamethylcholine hydrochloride (mecholyl) as a parasympathetic stimulant, atropine as a parasympathetic depressant or presacral sympathectomy

In our own practice (working with Lewis and Langworthy) cystometric study of the frequency of appearance of urinary retention, partial or complete, during treatment of apparently uncomplicated dementia paralytica by induced fever has brought out the fact that involvement of the spinal cord (i e, the tabetic form of dementia paralytica) must be far more common than is usually suspected

The practical value of cystometry, while perhaps familiar enough to neurologists and urologists, has apparently not yet received the attention it deserves from internists and syphilologists

Pathology of Dementia Paralytica—In an excellent article Galbraith¹⁶⁰ reviews the pathology of dementia paralytica. He concludes

the histopathological conception of general paralysis has been considerably extended. Notable additions to our knowledge of the morphological aspect of the process have been created by the discovery of the iron reaction, by the finer and more selective methods of demonstrating the glial elements, and by further studies of atypical forms of the process

In general paralysis there are many problems awaiting our attention. Although general paralysis may be one of the best known diseases from the histologic aspect, yet the origin of the psychologic manifestations, apart from the gross dementia due to cortical destruction in the later stages, is as obscure as in the functional psychoses. The exact circumstances of the invasion of the nervous parenchyma have yet to be elucidated, and it is unknown what factor is responsible for the breach in the "hæmato-encephalic" barrier. Further, we have no explanation for the constant and characteristic distribution of the disease process. The rôle of the spirochæte [in the development of certain pathologic changes] has been neither satisfactorily assessed nor eliminated. [Nor has it been explained] why it eludes demonstration in certain cases where there is other undoubted evidence of an active stage of the disease. The exact nature of the iron reaction, which is evidently unknown in other organs affected by syphilis, also merits considerable attention.

The possibilities of purely histologic research are by no means exhausted, and there is yet much scope in the direction of thorough and systematic examinations of the entire nervous system. Finally the most promising avenue will eventually prove to be the co-operation of the histologist and the bacteriologist in experimental studies upon the spirochæte

160 Galbraith, A. J. Some Problems in the Histo-Pathology of General Paralysis of the Insane, Brit J Ven Dis **14** 197 (July) 1938

Treatment of Neurosyphilis—(a) *Tabes Dorsalis* In a paper important both for the large number of patients studied and for the statistical details, O'Leary and the Cooperative Clinical Group¹⁶¹ have analyzed the outcome of treatment in 985 patients with *tabes dorsalis*. They summarize their conclusions as follows:

Diagnosis—(a) *Blood* Thirty-two percent of the patients with *tabes dorsalis* had a negative blood Wassermann reaction and a positive spinal fluid at the time the diagnosis was made. When the blood Wassermann reverses to negative the likelihood of clinical improvement is greater than when the Wassermann remains positive, and clinical progression is more likely if the serology is constantly positive. A relapse of the blood Wassermann from negative to positive is accompanied by a similar relapse of the spinal fluid in 29 percent of the cases. The blood Wassermann reaction is an inefficient guide in the treatment of *tabes dorsalis*.

(b) *Spinal fluid* The degree of abnormality of the spinal fluid indicates with a fair degree of accuracy the prognosis and in addition serves as a guide in estimating in advance the intensity, duration, and type of treatment indicated. Spinal fluids with the milder degrees of abnormality respond more satisfactorily, more quickly, and more permanently than do those with the severe grades of positivity. Treatment failures, as evidenced by clinical progressions, were more common in the cases with severe degrees of spinal fluid involvement. Clinical arrest may occur even though the spinal fluid remains positive, and, on the other hand, clinical progression may continue in the presence of completely negative blood and spinal fluid reports. Nevertheless the best results were noted in the majority of patients who obtained complete serologic reversals to negative.

(c) *Blood versus spinal fluid* Of the tabetics who had never been treated for syphilis, 31 per cent had a negative blood and a positive spinal fluid reaction at the time of the original examination. In 5 percent of the tabetics not previously treated for syphilis, both the blood and spinal fluid were completely negative. A spinal fluid that vacillates between negative and positive offers a better prognosis than a spinal fluid that remains persistently positive, because in this latter group clinical progression developed in one-quarter of the cases. When the blood and spinal fluid were both reversed, 38 per cent showed symptomatic recovery, when the spinal fluid reversed and the blood was unchanged clinical arrest occurred in 24 percent, when the spinal fluid remained positive and the blood serologic reactions became negative symptomatic recovery was noted in 17 percent, and when both blood and spinal fluid remained positive clinical recovery was noted in 15 percent. A study of clinical progression showed that when the blood and spinal fluid remained positive 20 percent progressed and that when both tests were completely negative only 3 per cent developed advanced signs of the disease.

Treatment—(a) *Serology* An accurate comparative appraisal of the numerical value of routine treatment, intraspinal treatment, malaria therapy, and trypanamide was not feasible in this material, some pertinent facts, however, were elicited about the four therapeutic procedures. The treatment of *tabes* must be individualized because in certain patients excellent results are obtainable after a few

161 O'Leary, P. A., Cole, H. N., Moore, J. E., Stokes, J. H., Wile, U. J., Parran, T., Vonderlehr, R. A., and Usilton, L. J. *Tabes Dorsalis*. Cooperative Clinical Studies in the Treatment of Syphilis, *Ven Dis Inform* 19:367 (Nov) 1938.

injections of arsphenamine and a heavy metal. In others the intensive use of chemotherapy and perhaps the addition of one or two of the supplemental measures is necessary to arrest the process, while in some patients the intensive and prolonged use of the specific as well as the nonspecific methods will fail to control the disease.

In 60 percent of a group of 266 patients who received only routine treatment the spinal fluid became negative. However, of the 396 patients who were started on routine treatment in only 29 percent was the spinal fluid reversed, and of the group in whom reversal failed to occur 173 were given intraspinal therapy which was followed by serologic negativity in 53 percent. In other words, intraspinal therapy was successful in reversing the spinal fluid in more than one-half of those in whom routine treatment failed. In another group of 66 patients tryparsamide was successful in reversing the spinal fluids in 29 percent after routine and intraspinal therapy had failed. Malaria therapy was given to 75 patients after the other supplemental methods had failed and in 35 percent of these the serology was reversed to negative. The value of the supplemental methods is further demonstrated by the fact that in 194 patients who failed to obtain serologic reversal from routine treatment the auxiliary measures were serologically successful in 51 percent. The majority of the reversals occur by the third year of treatment with the various treatment procedures with the exception of tryparsamide with which the maximum results are noted about the tenth year. If toward the end of the first year of treatment or after 20 injections of arsphenamine and twice as much heavy metal have been given and the spinal fluid is unchanged, the supplemental treatments should be given, bearing in mind that intraspinal therapy will produce serologic reversals in about one-half the time that tryparsamide requires, and furthermore that malaria therapy will reverse the serology in one-third of the cases in which routine intraspinal therapy and tryparsamide have failed.

(b) Clinical results. The best clinical results were noted in those patients in whom the manifestations of tabes were of recent appearance, in whom the syphilis was of less than 10 years' duration, and who obtained reversals of the blood and spinal fluid to negative. The less abnormal the spinal fluid the better were the clinical results, and to obtain successful results from routine treatment more than 20 injections of arsphenamine and twice as much heavy metal should be given. Of the 286 patients who received only routine treatment clinical arrest appeared in 15.4 percent, while in 25 percent of 281 patients who did not show a definite clinical improvement on routine treatment the use of intraspinal therapy produced clinical arrest. Tryparsamide under similar circumstances produced decided clinical improvement in 26 percent, and malaria therapy was likewise successful in 20.5 percent. When a study was made of the influence of the various schemes of treatment on clinical progression it was found that in a group of tabetics who were receiving various types of treatment clinical progressions appeared in 30 percent, when intraspinal therapy was added the incidence of clinical progressions dropped to 8 percent. Malaria decreased progressions from 16 percent to 11 percent and tryparsamide did not exert any material influence in this regard.

Clinical progressions were noted in 14 percent (139) of the entire group of 968 tabetics. Advanced forms of tabes dorsalis, general paralysis, taboparesis, and vascular neurosyphilis were the most common types of progression noted. In those who had the Group III type of spinal fluid the majority of the clinical progressions were to general paralysis, while in most of those who had the Group

II type of fluid advanced signs of tabes dorsalis developed. In 15 percent of the patients who had a negative spinal fluid at the time the diagnosis of tabes was made clinical progressions occurred.

In this material the clinical response was usually preceded by the serologic reversal, however, the proportion of cases which obtain neither a clinical nor serologic response increases with the severity of involvement of the spinal fluid. Although clinical arrest was accompanied by serologic reversal in 70 percent it is to be noted that clinical progression may also appear in the presence of spinal fluid negativity. In 13 percent who did not obtain serologic reversal clinical arrest was noted, hence spinal fluid findings in tabes dorsalis do not always parallel the clinical outcome of the case.

Symptomatology—The outstanding observations made on the influence of the various treatment methods on the symptoms of tabes may be briefly summarized as follows. In 13 percent of the patients with optic atrophy the vision was improved and in 36 percent the progressive loss of vision was stopped. Malaria therapy was more successful than the other therapeutic measures in controlling optic atrophy after the patients had been given moderate amounts of chemotherapy.

Charcot's joints were improved in 7 percent and arrest of the process was noted in 56 percent, none of the systems of treatment demonstrated any marked superiority in this manifestation of tabes. Twenty percent of the patients with Charcot's joints had negative blood and spinal fluid reactions.

Trophic ulcers were completely healed in 47 percent, with no outstanding benefit from any therapeutic measure.

Ataxia disappeared in 15 percent of the cases and in 41 percent it was materially improved, and although the results were about the same from the four methods of treatment there were fewer cases that showed an advance in the ataxia following intraspinal therapy.

The neuritic pains were the most frequent symptoms of tabes and they were completely overcome in 31 percent of the cases, while in 35 percent the severity and frequency of the pains were lessened. Routine treatment alone had a higher percentage of successful results than did any of the supplemental measures in that 32 percent of the patients had a complete disappearance of the pains following this type of treatment. Malaria therapy was the least successful in the control of this symptom due no doubt to the fact that it was employed in the cases in which the other methods had given no relief.

Gastric crises disappeared following treatment in 44 percent and were less severe in 25 percent. Routine treatment was again the most successful method of treatment.

Incontinence disappeared in 24 percent, while in 38 percent the complaint was improved. Malaria therapy was most successful in the control of this complication.

Diplopia was the most responsive symptom to treatment, as it disappeared in 83 percent of the cases and in the majority of the cases from routine treatment.

It will not be possible to estimate accurately the value of any specific or non-specific therapeutic program for tabes dorsalis until the incidence of cases is known in which the symptoms of the disease disappear spontaneously as well as those that progress to the end point. A study of the influence of treatment on the objective signs of the disease was not attempted.

Metildi,²⁹ aware of the fact that the cause of lightning pains in tabes dorsalis is unknown and that the lesion of the spinal cord is similar to one which may be produced in swine by a diet deficient in vitamin B₁, treated

6 patients suffering from the lightning pains of tabes dorsalis with thiamin chloride. From 10 to 20 mg of this substance was given intravenously at weekly intervals. There was definite symptomatic improvement in all.

Reese and Hodgson,¹⁶² in order to throw some light on the relationship of tabes dorsalis and vitamin B₁, have studied the blood, analyzed the gastric contents and determined the pyruvic acid on a group of patients with neurosyphilis. The incidence of achlorhydria in 168 patients with neurosyphilis was no greater than in nonsyphilitic patients of corresponding age groups. Studies of the blood and determinations of pyruvic acid were made on all neurosyphilitic patients who had achlorhydria. Their blood was normal, and the pyruvic acid levels were not significantly altered. In short, the authors were unable to demonstrate vitamin B deficiency in tabes dorsalis. However, they treated a group of tabetic patients with liver extract, vitamin B₁ and yeast and observed marked symptomatic improvement. These patients were not given antisiphilitic treatment. Ataxia diminished, sensory disturbances were symptomatically improved, and in 1 instance there was an increase in the size of the visual fields. The authors suggest that a partial explanation for involvement of the central nervous system in syphilis may be a deficiency of vitamin B₁ and that if the patient is saturated with this vitamin, the normal resistance of the tissues will return, thereby preventing further attack by *S. pallida*.

(b) Dementia Paralytica. Many articles continue to appear in the literature dealing with the late results of the treatment of dementia paralytica with malaria and with fever mechanically induced. The following references are representative.

Escher¹⁶³ reexamined 155 of 296 patients with this disease who were treated with malaria from 1922 to 1934. Sixteen were fully recovered, 81 improved and 58 unimproved. Vervaeck¹⁶⁴ investigated the status of 83 such patients who had received malaria treatment ten years previously. The final outcome was favorable in 36 per cent. Taddei¹⁶⁵ reexamined 260 of 298 patients with dementia paralytica who had been followed for eleven years. He found 39 per cent cured, 26 per cent partially cured, 5 per cent unimproved and 14 per cent dead of the dis-

162 Reese, H. H., and Hodgson, E. R. Tabes Dorsalis and Vitamin B Deficiency, *Urol & Cutan Rev* **43** 56 (Jan.) 1939.

163 Escher, F. Nachuntersuchungen der in der Heilanstalt Burgholzli-Zurich von 1922-1934 mit Malaria behandelten Paralytiker, Schweiz Arch f Neurol u Psychiat **42** 37, 1938.

164 Vervaeck, P. Les chances de survie et de guérison des paralytiques généraux (80 catamnèses dix ans après la malarisation), *J belge de neurol et de psychiat* **38** 508 (July) 1938.

165 Taddei, G. Ghesite della paralisi progressiva curata con la malaria. Statistica dell'istituto psichiatrico di Firenze, *Riv di pat nerv* **51** 503 (May-June) 1938.

case Van der Heide ¹⁶⁶ analyzed the results in 274 patients treated with malaria. One fourth of the group had a complete recovery sustained over several years. The results were better in early dementia paralytica and in the expansive manic form. Huskisson ¹⁶⁷ presents the results in 300 patients treated with tertian malaria, 17 per cent recovered, 40 per cent improved, 30 per cent were not changed and 12 per cent died. Williams ¹⁶⁸ says that of the patients with dementia paralytica treated at the Indiana State Hospital during the fiscal year 1937-1938, 30 to 33 per cent improved, 30 to 40 per cent did not improve and 28 to 38 per cent died. Only about 12 per cent of the group could be discharged from the hospital.

(c) Gumma of the Brain. Alpers ¹⁶⁹ reports 3 cases of solitary gumma of the brain. There are no characteristic signs or symptoms except those of a tumor of the brain, and treatment is primarily surgical. Antisyphilitic treatment should, Alpers thinks, be delayed until after operation.

(d) Combined Fever and Chemotherapy in the Treatment of Neurosyphilis. Bennett and Lewis ¹⁷⁰ present data to show the superiority of a combination of fever and chemotherapy for neurosyphilis over either alone. Mapharsen or bismarsen (number of doses not stated) was given during the height of mechanically induced fever. Of 10 patients with late asymptomatic neurosyphilis, strongly positive findings in the cerebrospinal fluid were completely reversed in 7, partially reversed in 2 and unchanged in 1. Of 19 patients with dementia paralytica, complete remission with full occupational recovery followed in 14, moderate improvement in 3 and no improvement in 2. Of 31 patients with tabes dorsalis of the most severe type, many with resistant chronic symptoms, 16 (52 per cent) had complete relief of all predominating symptoms, 11 (35 per cent) had improvement in all predominating symptoms with disappearance of some of them, while only 4 were unimproved. Of 28 patients with neuritic pains, 24 were definitely benefited or relieved. Eleven of 15 patients with gastric crises were completely or partially

166 van der Heide, C. Malarial Therapy of General Paralysis, *Nederl tijdschr v geneesk* **82** 3331 (July 2) 1938.

167 Huskisson, D. S. Malarial Pyrotherapy for Syphilitic Disease of Central Nervous System, *South African M J* **12** 589 (Aug. 29) 1938.

168 Williams, C. L. Neurosyphilis, *J Indiana M A* **32** 62 (Feb.) 1939.

169 Alpers, B. J. Gumma of the Brain, *Am J Syph, Gonorr & Ven Dis* **23** 233 (March) 1939.

170 Bennett, A. E., and Lewis, M. D. The Prevention and Treatment of Neurosyphilis by Combined Artificial Fever and Chemotherapy, with Report of Results in Seventy-Two Cases, *Nebraska M J* **23** 295 (Aug.) 1938, The Prevention and Treatment of Neurosyphilis by Combined Artificial Fever and Chemotherapy, *Am J Syph, Gonorr & Ven Dis* **22** 593 (Sept.) 1938.

relieved Of 12 patients with severe, disabling types of meningovascular neurosyphilis, complete relief from predominating symptoms was secured in 10

These results are so far superior to any reported by other workers from fever therapy or chemotherapy alone, and are so in line with the experimental data now beginning to appear, e g, from Borchers,²⁶ as to suggest that further clinical and experimental studies in this important therapeutic field are urgently needed

(e) Aldarsone Kamman¹⁷¹ reports the use of aldaione, a new pentavalent arsenical (formaldehyde sulfoxylate of 3-amino-4-hydroxyphenylarsonic acid), in the treatment of 53 patients with neurosyphilis The drug was found to be relatively nontoxic Kamman feels that the drug is an effective agent in the treatment of neurosyphilis

(f) Malaria Milam and Kusch¹⁷² have treated 29 white and 6 Negro patients with *Plasmodium knowlesi*, the malarial parasite responsible for spontaneous malaria in apes All of the white patients were susceptible to the organism, but none of the Negroes responded The infection was at times quite heavy, more than 1 per cent of the red blood cells being parasitized Relapses were not infrequent

Sioli, Kentenich and Boldt¹⁷³ describe in detail the technic for the cultivation of mosquitoes (*Anopheles*) to be used in the malarial treatment of dementia paralytica They have collected 27 different swarms of mosquitoes in the past three years, all of which successfully transmit malaria to human beings

Mayne and Young¹⁷⁴ combined *Plasmodium vivax* and *Plasmodium malariae* in the treatment of 16 patients suffering from dementia paralytica They observed that one of the strains became predominant, the other tending to disappear The predominant species was not the same in every instance, but was usually the tertian It is probable that the predominance of one strain over the other is not due to cross immunity

Boyd, Kitchen and Matthews¹⁷⁵ have demonstrated that there is no cross immunity between *P vivax* and *Plasmodium falciparum* They

171 Kamman, G R Intravenous Aldarsone in the Treatment of Neurosyphilis, *Am J Syph, Gonorr & Ven Dis* **22** 638 (Sept) 1938

172 Milam, D F, and Kusch, E Observation on *Plasmodium Knowlesi* Malaria in General Paresis, *South M J* **31** 947 (Aug) 1938

173 Sioli, F, Kentenich, A, and Boldt, E Weitere Erfahrungen über die Zucht der *Anopheles* und ihre Verwendung in der Malariabehandlung der Paralytiker, *Arch f Schiffs- u Tropen-Hyg* **43** 1 (Jan) 1939

174 Mayne, B, and Young, M D Antagonism Between Species of Malaria Parasites in Induced Mixed Infections Preliminary Note, *Pub Health Rep* **53** 1289 (July 29) 1938

175 Boyd, M F, Kitchen, S F, and Matthews, C B Consecutive Inoculations with *Plasmodium Vivax* and *Plasmodium Falciparum*, *Am J Trop Med* **19** 141 (March) 1939

inoculated patients with either *P. vivax* or *P. falciparum* and subsequently, during the incubation period, the period of acute attack or after recovery, inoculated them with the heterologous species. Inoculation with the heterologous strain during the acute attack or after recovery was successful in every instance. Inoculation with the heterologous species during the incubation period, however, gave negative results in 2 instances. The authors are unable to explain this observation but believe that it is not the result of antagonism between the two species. They feel that if there was antagonism, all superinfections with the heterologous strain should have been negative.

Goldman¹⁷⁶ reports the use of mapharsen in the treatment of 24 patients suffering from tertian malaria. One patient had spontaneous malaria, the remaining 23, malaria inoculata. The dose of mapharsen was 0.04 to 0.06 Gm. Fourteen patients received a single injection, 1 received four injections and 9 each received eleven injections. There were two recurrences, both in patients receiving one injection, and both responded to further treatment with mapharsen. The author believes that mapharsen has a definite place in the treatment of tertian malaria.

(g) Lumbar Puncture. In order to investigate the effect of lumbar puncture on the cerebrospinal fluid, Scheid¹⁷⁷ performed puncture and repuncture on 106 persons, 18 of whom had no clinical manifestations of disease of the central nervous system. In the cerebrospinal fluid of 16 of the 18 normal persons there was an increase in lymphocytes at the time of the second puncture (two to four days after the first puncture) but no change in total protein, globulin, sugar or mastic reaction. Cerebrospinal fluid which was abnormal at the time of the first puncture showed a less marked increase in lymphocytes and a slight decrease in total protein, globulin, sugar and mastic reaction at the time of the second.

SYPHILIS AND PREGNANCY

Incidence of Syphilis in Pregnant Women and Stillborn Infants—Harrington and Matschat¹⁷⁸ show that there has been a significant decrease in the incidence of syphilis in pregnant women in a large New York Clinic during the period from 1914 to 1937. Of 5,500 women examined before September 1923, 7.58 per cent had positive routine serologic tests for syphilis, of 4,422 examined from 1923 to 1937, only 4.36 per cent had positive tests.

176 Goldman, D. The Use of Mapharsen in the Treatment of Malaria, *Am J M Sc* **196** 502 (Oct.) 1938.

177 Scheid, W. Ueber Liquorveränderungen nach der Lumbalpunktion, zugleich ein Beitrag zur Frage der postpunktionellen Symptome, *Ztschr f d ges Neurol u Psychiat* **163**.397, 1938.

178 Harrington, H., and Matschat, L. J. Syphilis in Dependent Mothers, *Am J Syph, Gonorr & Ven Dis* **22** 513 (July) 1938.

Montgomery¹⁷⁹ investigated the cause of 449 stillbirths in Philadelphia. Syphilis was found to be the cause of 24 (9 per cent). Twenty of these could have been prevented. Of 49 instances in which the cause of stillbirth was unknown, serologic tests were done on the mother in only 15.

Placental Transmission of Arsenic—Various workers have shown that after the administration of an arsenical to a pregnant woman or animal the drug can be readily demonstrated in the placenta, particularly the fetal portion, but is present only in minute quantities in the blood and organs of the fetus. Snyder and Speert¹⁸⁰ have investigated further the transmission of arsenic to the fetus. They gave single injections of neoarsphenamine to rabbits in different stages of pregnancy and calculated the arsenic present in the fetus and in the placenta. Arsenic could not be demonstrated in the fetus until the beginning of the latter half of pregnancy. The placenta contained eighteen times as much arsenic as the fetus, and the fetal portion of the placenta contained six times as much arsenic as the maternal portion. Two conclusions drawn by the authors were

Variations in the arsenic content of the placentas could not be correlated with the stage of pregnancy.

The concentration of arsenic in the fetus near term approaches the level calculated to be present in the maternal tissues when definite antisyphilitic effect is exerted.

Treatment—Costello and associates¹⁸¹ analyzed the outcome of pregnancy in 116 syphilitic mothers treated with mapharsen. Bismuth preparations were given to these patients concurrently. These women gave birth to 106 (91.4 per cent) living infants. Of 72 women who received six or more treatments, 94.7 per cent had living children. Of the 106 babies born alive, 50 were followed in the pediatric clinic, and 5 (10 per cent) of these had positive results from the Wassermann test. The authors then compare the results obtained with mapharsen with those obtained with a bismuth preparation alone, with neoarsphenamine and with acetylarsan (p-oxyacetylaminophenylarsinate of diethylamine). They find that fewer syphilitic children are born alive after treatment with neoarsphenamine than after treatment with mapharsen plus a

179 Montgomery, T. L. Problems in the Etiology and Prevention of Stillbirths, *Am J Obst & Gynec* **36** 975 (Dec.) 1938.

180 Snyder, F. F., and Speert, H. The Placental Transmission of Neoarsphenamine in Relation to the Stage of Pregnancy, with Special Reference to the Prenatal Treatment of Syphilis, *Am J Obst & Gynec* **36** 579 (Oct.) 1938.

181 Costello, M. A., Coppolino, J. A., Rakoff, A. E., Roeder, P. H., and Dickson, G. S. Mapharsen in the Treatment of Syphilis Complicating Pregnancy: A Comparative Study, *Am J Syph, Gonorr & Ven Dis* **23** 332 (May) 1939.

bismuth preparation or with acetylarsan. The percentages, in the order of the drugs named, are 32, 10.07 and 38.4.

In evaluating these drugs in terms of living births, they find that after six or more doses, respectively, of quinine bismuth iodide, maphaisen plus bismuth, acetylarsan and neoarsphenamine the percentages of living children are, in the order of drugs named, 80, 94.4, 96.5 and 96.7. A control series of 65 untreated mothers had only 69.1 per cent living children.

CONGENITAL SYPHILIS

Pathologic Observations—Orsós¹⁸² describes what he believes to be the first case of syphilitic changes in a 4 week old embryo to be reported. A 17 year old girl under treatment for secondary syphilis aborted. In the aborted material was found a 4 week old embryo. Sections of the embryo revealed a pathologic change of an inflammatory nature in the region where the neck would later develop. In spite of the fact that no *S. pallida* could be demonstrated in this lesion, the author assumes that it was due to syphilis.

Carnevale Ricci¹⁸³ examined histopathologically the ears of 43 congenitally syphilitic infants. Some were stillborn at term, and others died a few days to two months after birth. He found definite syphilitic changes in the ears of 8 of the 43 infants examined. Syphilitic lesions of all degrees of severity and in all stages of development were found in all parts of the ear. The labyrinth was most commonly affected, and both the bony and the membranous capsule were involved. The aural lesions were generally associated with severe syphilitic changes in other parts of the body and many of the infants had syphilitic meningitis. There are excellent photomicrographs, including several colored plates.

D'Aunoy and Pearson¹⁸⁴ were able to find congenital syphilitic lesions of the intestine in 3 (13 per cent) of 230 children with congenital syphilis who were examined post mortem. In each instance *S. pallida* was demonstrated in the lesions. The authors conclude from their personal experience and from a review of the literature that more than 75 per cent of congenital syphilitic intestinal lesions are in stillborn infants and children who live less than twenty-four hours. The most characteristic intestinal lesion is a raised yellow plaque-like band encircling the bowel, which is usually found in the lower portion of the ileum. There is necrosis of the mucosa and submucosa. When spirochetes are

182 Orsós, I. J. Syphilitische Veränderungen an vierwöchigem Embryo, Arch f Dermat u Syph **178** 188, 1938.

183 Carnevale Ricci, F. Osservazioni istopatologiche sulle sifilide congenita dell'orecchio, Arch ital di otol **50**:521 (Oct) 1938.

184 D'Aunoy, R., and Pearson, B. Intestinal Lesions in Congenital Syphilis. Histologic Study with Report of Three Additional Cases, in All of Which Spirochetes Were Identified, Arch Path **27** 239 (Feb) 1939.

found, they are most prominent in the perivascular tissue and in the walls of the blood vessels. If present in the muscle coats, they tend to lie in the direction of the muscle fibers.

Diagnosis—In a paper which is notable for clear thinking and calm presentation of a subject which too frequently previously has inspired other authors to the contrary, Black¹⁸⁵ considers the criteria on which a diagnosis of congenital syphilis properly should be based. In the days before antisyphilitic treatment of pregnant women with syphilis was general, congenital syphilis was both common and severe in the infants born of these women. At present, however, many pregnant syphilitic women have had some prepartum care, which may have prevented or may have “cured” fetal infection. In some instances, however, it has served only to suppress the manifestations of syphilis in the newborn.

Black says, therefore

The diagnosis of congenital syphilis, once concerned principally with severe and relatively easily recognized cases, has been rendered much more difficult as a result of the nearly universal use of ante-partum treatment in infected women. A more refined and judicious use of diagnostic methods is necessary now in order to identify the occasional mildly infected infant among the many syphilis-like babies born of treated syphilitic mothers. Coincident with the diminished frequency and severity of congenital syphilis, there must come a change in attitude toward the newborn babies of syphilitic women. Whereas previously the baby was properly considered probably syphilitic, now the infant may be regarded as nonsyphilitic until proved otherwise. At one time it was perhaps excusable to give antisyphilitic treatment to all babies born of syphilitic women, only the exceptional infant was unjustly exposed to the dangers and disadvantages of unnecessary treatment. Such an attitude now would be an injustice to most of the babies.

There are three main methods of investigation by which the unquestionable presence or absence of congenital syphilis in living infants or children may be definitely determined:

- (1) bacteriologic examination
- (2) serologic examination
- (3) roentgenologic osseous examination

By the term “bacteriologic examination,” the author means a search for *S. pallida* by dark field examination of material from the umbilical vein and from “suspicion arousing” lesions or abnormalities such as failure of the umbilical stump to heal.

As to serologic examination, the author states

There is overwhelming evidence that _____ reagin may be present in the circulating blood of newborn infants born of syphilitic mothers without the concomitant presence of spirochetes in the infant's tissues. Presumably the

185 Black, W. C. Diagnosis of Congenital Syphilis. Pathognomonic Criteria, *J. Pediat.* **14** 761 (June) 1939.

reagin, crosses the placental barrier from the maternal to the fetal blood. Thus a nonsyphilitic newborn infant may have a positive blood [serologic] test.

In the asymptomatic syphilitic infant reagin may be entirely absent at birth, but it will be present within a few weeks or at most within four months. More commonly the first serologic test will be positive. The reagin responsible for this early positive test may be either maternal or fetal in origin or may be a mixture of both. In general, titers tend to be higher in infected than in uninfected infants. If the cord blood reagin titer exceeds by a wide margin the maternal level, one cannot escape the probability that the infant is syphilitic. There is as yet not enough clinical support to consider this observation of pathognomonic significance. Serologic differentiation between the infected and noninfected newborn infants depends, in our present state of knowledge, upon an increase in the amount of the reagin in the infected baby.

Roentgenologic findings, in the very nature of the case, are a much less direct evidence of the presence of a disease such as syphilis than is the identification of the causative organism or a specific serologic reaction. Considering the recent confusion caused by the deposition of bismuth lines in the long bones of infants whose mothers have been treated with a preparation of this metal during pregnancy, Black recognizes the present unsettled state of roentgenologic diagnosis. However, from his study of 102 cases of congenital syphilis, among which, judged by a mortality rate of 42 per cent, the average intensity of infection was great, he lists ten types of roentgenologic osseous change which he considered diagnostic of congenital syphilis.

- 1 Well-defined saw-tooth metaphysis in well calcified bones
- 2 Deep zones (in the longitudinal axis) of submetaphyseal rarefaction
- 3 Multiple "separation of epiphyses" with or without impaction in bones which are not rachitic
- 4 Bilateral symmetrical osteomyelitis of the proximal mesial aspects of the tibiae
- 5 Multiple circumscribed osteomyelitis of the long bones shown by the roentgen rays as patchy areas of rarefaction
- 6 Multiple longitudinal areas of rarefaction (osteomyelitis) in the shafts of the long bones, sometimes resulting in fractures
- 7 Destructive lesions at the mesial or lateral aspects of the metaphyses (foci of rarefaction)
- 8 Multiple areas of cortical destruction generally seen within a centimeter of the ends of the bones
- 9 Double zone of rarefaction at ends of bones
- 10 Localized periosteal cloaking occurring in more than one bone

He feels that criteria 1, 3, 4, 5, 6, 7 and 8 are still acceptable as pathognomonic. As he points out, however, a very high degree of technical perfection in the roentgenogram is necessary for unequivocal demonstration of criterion 1. In criterion 7 the changes should be multiple and very definite.

There is perhaps some question as to whether criteria 2, 9 and 10 are sufficiently reliable to retain their pathognomonic significance. As for criterion 2 we feel, that perhaps it should not be included in its present form as a sign by which a definite diagnosis of congenital syphilis can be made.

Black presents a schema of diagnosis, the use of which he feels will establish the presence or absence of syphilis in nearly all babies within three weeks after birth. Although he grants that there are perhaps occasional instances in which one would be justified in beginning treatment for syphilis in infancy without the support of an absolutely positive diagnosis, he holds that such action should be taken only after consultation with the best available authority in each of the fields concerned and that a sharp distinction should be drawn between a positive and a presumptive diagnosis. The procedure for the diagnosis of congenital syphilis in young infants was described by Black as follows:

- 1 Routine Wassermann test, history (with syphilis in mind), and careful physical examination (with syphilis in mind) of all pregnant women at the time pregnancy is diagnosed. Frequent check-ups of suspicious cases.

- 2 Suitable treatment of every pregnant woman who has or has had syphilis, regardless of the results of serologic tests, physical signs of the disease, or previous treatment.

- 3 Dark-field examination of umbilical vein scrapings in every case in which there has been inadequate, irregular, or no ante-partum treatment.

- 4 Cord or peripheral infant blood Wassermann or other serologic test in every case and titrations in all positive cases. Without this original test, titrated when positive, it is impossible to evaluate properly the next test.

- 5 Roentgenograms of the long bones within two weeks after birth of those infants in which the presence of syphilis is fairly probable (inadequate, irregular or no ante-partum treatment) or in which the first serologic reaction was positive.

- 6 Repeated infant blood Wassermann tests at not longer than two-week intervals with titrations in cases in which the original test was positive.

- 7 Repeated roentgenograms at one month or six weeks of age in cases in which the diagnosis is still in doubt.

- 8 Repeated dark-field examinations of any suspicious lesions (mucous membranes of nose, mouth, or anus, diaper rash, slowly healing umbilical stump etc.)

- 9 Spinal fluid examinations of infants in whom the presence of syphilis is fairly probable (see 5 above) when subsequent examinations have not revealed positive diagnostic results.

Congenital Syphilis as a Starting Point for Case Finding—In a discussion on the management of syphilis in pregnancy and the diagnosis of early congenital syphilis, Davis¹⁸⁶ calls particular attention to the importance of family case finding. In examining the families of 1,676 syphilitic mothers registered with the New York City Health

¹⁸⁶ Davis, M. L. Prevention of Congenital Syphilis, Arch. Pediat. **55** 590 (Oct.) 1938.

Department, she found 30 per cent of the persons examined to be infected. In two families alone, 13 of 16 living members examined had syphilis¹

Congenital Syphilis in One of Twins—Wile and Welton¹⁸⁷ present a review of the literature on syphilis in twins and report a thoroughly studied case of prenatal syphilis in one of fraternal twins

Ocular Lesions—McLeod¹⁸⁸ describes some of the less common findings in the eyes in congenital syphilis. Lesions of the fundus may be divided into four main types

Type I The so-called "salt and pepper" fundus with yellowish, or grayish red dots interspersed among a multitude of granular brown to black pigment dots. In the more severe forms the spots are larger and tend to invade the macular region, the nerve may be atrophic and vision impaired

Type II Larger and more irregular pigment masses occur, located mostly at the periphery, between which similar "bleached" areas appear. The nerve may be atrophic. Sidley-Huguemine has noted this type after the subsidence of interstitial keratitis

Type III Disseminated chorioretinitis. The lesions are round or oval and appear as an atrophic patch surrounded by a ring of pigment. The macula may be involved

Type IV Similar to retinitis pigmentosa and at times difficult to differentiate. The visual symptoms are identical. This type seems now to be rare

It is obvious that all these changes are dependent upon the migration of pigment consequent to inflammatory processes and as a natural result of the repair of localized lesions or in response to stimulation of the pigment cells as a part of the general defense mechanism of the body

Anderson and Wilson¹⁸⁹ report the results of treatment with induced fever in 22 patients with interstitial keratitis. Seven had received previous chemotherapy, 6 of whom had shown no improvement after two to five months of treatment, and 3 of whom had lesions develop in the other eye during treatment. The seventh had had several relapses during a four year period of therapy. In 13 patients the keratitis was acute and untreated. Of these, 3 were given fever by injecting vaccine intravenously, and 10 were treated with malaria. Two of the 3 patients treated with vaccine and all of the 10 treated with malaria showed a satisfactory immediate response. There were two relapses, one six and one ten weeks after the induction of malaria. Both responded to a few injections of vaccine. Nine patients with chronic interstitial kera-

187 Wile, U. J., and Welton, D. G. Prenatal Syphilis in One of Twins, *Am J Syph, Gonorr & Ven Dis* **22** 544 (Sept.) 1938

188 McLeod, J. The Eye in Congenital Syphilis, *J Missouri M A* **36** 49 (Feb.) 1939

189 Anderson, C. R., and Wilson, W. A. Active Interstitial Keratitis of Late Prenatal Syphilis. Its Treatment, *California & West Med* **50** 196 (March) 1939

titis were treated with fever. A satisfactory result was obtained in 3 with vaccine alone. Of the 6 remaining, 4 responded satisfactorily to malaria. The authors believe that their own results and those of other workers show that malaria is a valuable form of therapy in interstitial keratitis, particularly if followed by two years of chemotherapy.

Treatment—Howard¹⁹⁰ shows that, unless neurosyphilis is present, the long term outcome of treatment in congenital syphilis is extremely satisfactory. Forty-five children were followed for two to ten years (average five to six years) after the completion of treatment. A satisfactory result was obtained for 85 per cent of the entire group, the result being better in those treated during the first year of life. Twenty children (45 per cent) were "cured." Eighteen children (40 per cent) had at the end of the ten year period a positive Wassermann reaction of the blood as the only sign of syphilis. The poor clinical outcome in the remaining 7 children was explained by the presence of neurosyphilis in 6.

Epilepsy—Babonneix¹⁹¹ investigated the association of epilepsy with congenital syphilis. Of 246 patients with congenital syphilis, 22 per cent had epileptic attacks. Among 323 persons with epilepsy selected at random and not previously known to have syphilis, 17 per cent were found to have congenital syphilis.

Epiphysial Changes—Park and Jackson¹⁹² present a correlation of roentgenologic and necropsy observations in congenital syphilis. In some infants the cartilage is most affected, in others, the osteoblasts. In some, destructive processes are predominant, in others, new bone formation in the periosteum. These irregular projections are not always present in children with congenital syphilis.

Necropsy studies show that the roentgenologically visible projections into the cartilage at the ends of the long bones are around the nutrient vessels of the cartilage, the cartilage canals. In many cases the proliferated cartilage shows extreme degenerative changes. The fundamental anatomic lesions may lie either in the cartilage canals or in the cartilage itself. The cartilage in close proximity to the cartilage canals is more normal than that lying at a distance, matures more quickly, becomes calcified earlier and so produces the irregular spike formation.

190 Howard, P. J. Congenital Syphilis. A Ten Year Study of Forty-Five Children, *J. Pediat.* **14** 220 (Feb.) 1939.

191 Babonneix, L. Le rôle de la syphilis congénitale dans le déterminisme de l'épilepsie, *Acta pædiat.* **22** 47, 1938.

192 Park, E. A., and Jackson, D. A. The Irregular Extensions of the End of the Shaft in the X-Ray Photograph in Congenital Syphilis, with Pertinent Observations, *J. Pediat.* **13** 748 (Nov.) 1938.

Serologic Changes—Davies¹⁹³ carries further the work of Faber and Black¹⁹⁴ and of Christie¹⁹⁵ on a quantitative technic for testing the blood of infants of syphilitic mothers as an aid in differentiating syphilitic from normal children. Christie followed a group of newborn infants for four months and observed that infants whose blood tests, positive at birth, became negative and remained so presented subsequently no signs of syphilis but that infants whose tests showed an initial drop in titer and then a sudden rise showed later other signs of syphilis. Davies followed 56 infants for longer periods of time, 20 of them for one year. Of the 56 infants, 25 had positive neonatal blood tests, only 2 of these later showed congenital syphilis. Nineteen infants whose neonatal blood tests were negative were followed for six months, and 12 of the 19 were followed for one year, congenital syphilis developed in none.

In most instances the neonatal positive blood reactions (representing, of course, transfer of reagin from mother to fetus) diminished or disappeared within two weeks, but in 1 case the positive reaction remained for forty days and in another for three months. Davies suggests that inasmuch as congenital syphilis is more likely to develop in infants who have positive neonatal tests than in those whose tests are negative, infants with positive tests should be followed more closely and for a longer period of time.

Oral Treatment with Acetarzone—One of the best of recent papers on the administration of acetarzone by mouth in the treatment of congenital syphilis is that of Pillsbury and Perlman¹⁹⁶. Since 1931 these authors have treated 196 patients with this drug, for 187 of whom the diagnosis of syphilis seems certain. This group of 187 patients has been followed for periods varying from two months to six and a half years, and the observations form the basis of the present report. Of this number, 145 have been followed for more than one year, 116 for more than two years and 87 for more than three years since the institution of treatment. In 87 patients in this series syphilis was not diagnosed in the dispensary at the examination on admission and was

193 Davies, J. A. V. The Evaluation of Serologic Tests for Congenital Syphilis, with Special Reference to the Neonatal Period, *J. Pediat.* **13**:341 (Sept) 1938.

194 Faber, H. K., and Black, W. C. Quantitative Wassermann Tests in the Diagnosis of Congenital Syphilis. Clinical Importance of Fildes' Law, *Am. J. Dis. Child.* **51**:1257 (June) 1936.

195 Christie, A. U. Diagnosis of Syphilis in Newborn Infants. Use of Quantitative Wassermann Tests, *Am. J. Dis. Child.* **55**:979 (May) 1938.

196 Pillsbury, D. M., and Perlman, H. H. Acetarzone Therapy in One Hundred and Eighty-Seven Cases of Congenital Syphilis, with Observations on a Group of Eighty-Seven Patients Receiving No Treatment, *Arch. Dermat. & Syph.* **39**:969 (June) 1939.

not discovered in subsequent examinations until, on an average, three years after admission. This group of patients, therefore, was one in which the course of the untreated disease could be observed, and the delay in the recognition of the disease explains why, although the average period of observation of the group of patients was four and four-tenths years, the average period of observation after treatment was begun was only two and eight-tenths years.

The authors are impressed with the clinical effects of treatment with acetarsonic acid. In the 3 patients who were so studied the spirochetes disappeared from surface lesions in seventy-two, ninety-six and one hundred and twenty hours, respectively. In general, cutaneous lesions healed within three or four weeks, osseous lesions responded satisfactorily, and in 2 patients with Clutton's joints involution occurred. They observed no instance of late clinical relapse after treatment with acetarsonic acid, and clinical progression in spite of treatment occurred in only 8 cases. The effect of the drug on interstitial keratitis was, however, disappointing.

A very satisfactory incidence of serologic reversals was obtained, i. e., 70 per cent reversals in children whose treatment was instituted before they were 6 months of age, and 36 per cent reversals in children who were more than 6 months of age when treatment was begun. The authors point out, however, that this is less frequent serologic reversal than that reported by Smith for children treated with alternating courses of a bismuth preparation and an arsphenamine. They do not, however, consider the possible effects of differences in the serologic laboratories and in the sensitivity of the serologic tests employed.

Their experience with the incidence of reaction emphasizes one of the aspects of any method of oral treatment for syphilis which is extremely distressing, i. e. Can the parents or guardians be depended on to administer the drug with the regularity which is so necessary? With the therapeutic system which they were using, Pillsbury and Perlman found that some type of reaction developed in 32 per cent of children being treated with acetarsonic acid in the hospital wards whereas only 8 per cent of those whose treatment was being prescribed in the outpatient department, to be carried on at home, suffered the same fate. Since they could find no other factor to explain so wide a difference in the incidence of reactions, they were forced to conclude that the basic dose which they employed was perhaps too high and that the children being treated in the hospital were receiving it as prescribed while those being treated in the outpatient department were not. Concerning this they say

We cannot but feel, however, that a specter is always present—that the entrusting of treatment to a prescription blank may shift the responsibility for treatment of an entirely helpless and dependent child to the hands of an irrespon-

sible parent or guardian. It is true that one can sense the irresponsible parent quickly, and we believe that he is an absolute contraindication to further acetarsone therapy. The child with congenital syphilis has already paid too great a price for the irresponsibility of one of his parents, no more should be expected of him.

The cerebrospinal fluid was examined in 102 cases, with positive results in only 2, in 2 others, however, there were clinical signs of neurosyphilis. In 1 of these there was said to have been an abnormal reaction of the cerebrospinal fluid previously.

In the discussion the authors point out that there is no adequate experimental background for the determination of the toxicity and spirocheticidal effect of individual lots of acetarsone. This is due, in part at least, to differences in the factors which influence absorption from the gastrointestinal tract of man and of experimental animals, but other reasons are probably also involved. They feel that acetarsone by mouth is an active antisyphilitic agent, which is, however, less rapid in its action than arsphenamine. In clinical use they feel that a dosage based on weight is essential, but even with such a dosage reactions are not entirely prevented. Nephritic reactions occurring insidiously and suddenly are the greatest single drawback to treatment with acetarsone, and it is strongly believed that administration of the drug should not be resumed after such a reaction.

The authors summarize the objections to this method of treatment as follows:

The effect of acetarsone in arresting congenital syphilis is inferior to that of arsphenamine and bismuth preparations. The incidence of reactions is high, acetarsone cannot be controlled by experimental studies of spirocheticidal action and toxicity in animals, and administration to outpatients is not assured.

ACQUIRED SYPHILIS IN CHILDREN

From several large eastern clinics Smith¹⁹⁷ has collected 125 cases of acquired syphilis in children, 10 years of age or younger, and has analyzed them from the standpoint of mode of infection. This was attempted sexual intercourse in 43, kissing in 15, household contact in 14, transfusion in 9 and unknown (no data) in 44. Forty-five of the 125 children were admitted, from 1920 to 1937, to the pediatric clinic of the Johns Hopkins Hospital. Comparing this number with the 1,025 admitted for congenital syphilis over the same period, he finds the ratio of acquired to congenital syphilis in children under 10 years of age to be 1:23. Again comparing this group with the 4,487 patients with early syphilis admitted to the clinic for adults he finds that the ratio of acquired syphilis in children to that in adults is 1:100. Acquired

197 Smith, F. R., Jr. Acquired Syphilis in Children. An Epidemiologic and Clinical Study, *Am J Syph, Gonorr & Ven Dis* 23:165 (March) 1939.

syphilis is probably more common in children than is suspected Waugh¹⁹⁸ also reviews the literature on acquired syphilis in children and analyzes the data on 35 children seen from 1931 to 1936 in the venereal disease clinic of the United States Public Health Service at Hot Springs, Ark. Twenty-two children were between 5 months and 10 years of age, 2 were 11 years old, and 11 were 12 to 14 years of age. Only 2 of the group between 5 months and 11 years of age acquired syphilis through sexual intercourse, but all of the age group from 12 to 14 years of age acquired the disease through sexual exposure. Schoch and Long¹⁹⁹ report the observation of acquired syphilis in 4 sisters 6, 8, 9 and 11 years of age. All acquired syphilis from sexual exposure to the same 17 year old boy.

SYMPOSIUM ON SYPHILIS

At the 1938 meeting of the American Association for the Advancement of Science in Indianapolis, there was presented a symposium on syphilis consisting of thirty papers which have subsequently been published in monograph form²⁰⁰. Since the essayists in this symposium addressed themselves to reviews of assigned topics, there is comparatively little emphasis on the presentation of original investigation. A bibliography of each paper presented is therefore not supplied, though the symposium, both because of its distinguished contributors and because of the nature of their contributions, is in itself a valuable review of the literature of syphilis.

A general introduction to the symposium and some consideration of the biology of syphilitic infection were provided by Chesney. Holcomb presented the evidence against the American origin of syphilis, and Pusey defended the opposite point of view. The perennial debate as to the identity of syphilis and yaws was continued, with Butler upholding the affirmative and Fox the negative. Hudson discussed the significance of bejel. Ingraham's paper was concerned with *S. pallida* and the etiology of syphilis, while Olsen discussed the life cycle of *S. pallida*. Turner presented a description of the interrelationship between *S. pallida*, *Spirochaeta pertenuis* and *Spirochaeta cuniculi*.

A description of experimental syphilis and of the transmission of the disease to animals and their clinical reaction to it was in the capable hands of Pearce, while Beerman discussed the problem of treatment-resistant strains of *S. pallida*.

198 Waugh, J. R. Acquired Syphilis of Infancy and Childhood. Report of Thirty-Five Cases, *Am J Syph, Gonorr & Ven Dis* **22** 607 (Sept) 1938.

199 Schoch, A. G., and Long, W. E. Acquired Syphilis in Children. Case Reports on Four Sisters, *Am J Syph, Gonorr & Ven Dis* **23** 186 (March) 1939.

200 Moulton, F. R. Syphilis, Occasional Publications of the American Association for the Advancement of Science, no. 6, Lancaster, Pa., The Science Press, 1938.

Eagle and Mendelsohn presented a summary of Eagle's work on the spirocheticidal action of the arsphenamines on *S. pallida* in vitro. The immunity acquired in patients and the resistance acquired in the rabbit were the subject allotted to Kemp, while Michelson presented the newer conceptions concerning the pathologic aspects of syphilis.

From the clinical standpoint there were discussions of (1) methods for estimating the outcome of neurosyphilis (by O'Leary), (2) syphilis in pregnancy (by Beckh and Daily), (3) congenital neurosyphilis (by Dennie), (4) cardiovascular syphilis (by Scott) and (5) the clinical aspects of syphilis in diagnosis (by Senear).

The serologic aspects of the disease were not slighted, and the present status of serologic tests for syphilis was described by Hartman and Yagle, while the inseparable serologic twins, Kahn and Kline, discussed, respectively, outstanding features of the Kahn antigen, and the Kline antigen for the microscopic slide precipitation tests for syphilis. Kolmer's paper, however, was devoted not to a consideration of his own test but to serologic reactions in general and immunity in relation to cussed, respectively, outstanding features of the Kahn antigen, and the

From the therapeutic standpoint, Solomon discussed problems in specific and nonspecific treatment of neurosyphilis, Tatum devoted himself to some of the aspects of the chemotherapy of syphilis, and Wieder described the clinical status of the antisyphilitic drugs.

Untoward reactions to treatment were discussed by Kampmeier, and D. C. Smith attempted to evaluate the role of intercurrent infections in untoward cutaneous reactions following the administration of arsphenamine.

The papers on the public health aspects of syphilis control were contributed by Wile and Parran.

The volume in which this symposium is published is a valuable addition to the library of any physician particularly interested in the field of syphilis.

News and Comment

GENERAL

Directory of Medical Specialists—The first edition of the *Directory of Medical Specialists*, listing approximately 14,000 specialists certified by the twelve American boards and the two affiliate boards in the specialties, will be issued by the Advisory Board for Medical Specialties in December. It will be the official publication of the American Board for Medical Specialties and will contain, without expense to them, only the names of those specialists who have been certified by the American boards. It is expected that the directory will be issued every two years.

The directory will contain three sections: (1) a brief description of the Advisory Board for Medical Specialties, its organization and its objectives, (2) a description of the individual boards, with a geographic and a detailed biographic listing of their diplomates, the requirements for admission to their examinations for certification, the details of their organization and other general information, and (3) a complete alphabetic list of all 14,000 diplomates, with their addresses and indications of certification in their specialties.

The editorial board consists of the secretaries of the fourteen American boards. Dr. Paul Titus, 1015 Highland Building, Pittsburgh, secretary of the Advisory Board for Medical Specialists, is the directing editor.

The project is not designed to be profit making, hence the subscription price has been set at \$3.50 a copy, which is computed to cover only publication expenses. Subscriptions may be sent to the publication office, Columbia University Press, 2960 Broadway, New York, or to the office of the directing editor.

Notices

CUMULATED INDEX OF THE ARCHIVES OF INTERNAL MEDICINE

Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed \$5 a copy. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

I SHOULD BE WILLING TO SUBSCRIBE TO A CUMULATED INDEX OF THE ARCHIVES OF INTERNAL MEDICINE AT \$5.00

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DATE

Fundamentals of Internal Medicine By Wallace Mason Yater, A B, M D, M S (in Medicine), Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine, Physician in Chief, Georgetown University Hospital, Physician in Chief, Gallinger Municipal Hospital, Washington, D C, and Former Fellow in Medicine, the Mayo Foundation, Rochester, Minn, and collaborators Cloth Price, \$9 Pp 1021 with 255 illustrations and charts New York D Appleton-Century Company, Inc, 1938

During the past few years a number of textbooks of internal medicine have been presented to the medical profession All of them represent a great deal of painstaking work and meticulous attention to detail on the part of the authors Many of them have been good—most of them acceptable—but is this effort worth the result that is attained? Is there need for this multiplicity of textbooks of internal medicine? By what criteria shall we rank one above the other?

Dr Yater states that this book is "designed primarily for the introduction of students to the subject of internal medicine" This, of course, must be the function of all such textbooks, and it is the necessity for brevity that makes the selection of material so important If this necessity is kept in mind, Dr Yater has compiled a good book

It is written in semioutline form, and the important data are set in heavy black type Each section of the book is preceded by an outline of the material contained therein and is followed by a list of recommended texts for additional reading It is this extreme condensation of material that constitutes the greatest objection to the work Most of the important points dealing with any disease are mentioned, but they are not and cannot be adequately discussed Syphilitic heart disease is covered in three pages Pulmonary tuberculosis receives twenty pages—a generous allowance Diabetes mellitus is discussed in five pages

By way of contrast, almost one quarter of the book is devoted to a consideration of nervous and mental diseases and diseases of the eye and ear In view of their adequate treatment elsewhere, one wonders if these subjects should be granted a place in a textbook of internal medicine

It is, perhaps, unfair to direct all this criticism at Dr Yater's book when it is equally applicable to similar books As an outline of internal medicine the work is excellent An adequate discussion of disease will not be found here One cannot help but feel that Dr Yater's unusual ability should have been employed to better advantage than in the production of just another textbook of internal medicine

Insulin Its Chemistry and Physiology By Hans F Jensen, Ph D Price, \$2 Pp 252 New York Commonwealth Fund, 1938

This monograph is a timely and important addition to the literature on insulin and carbohydrate metabolism The purpose of the author, as stated in the preface, was "to give a comprehensive review of the latest developments in the chemical and physiological investigations of insulin" This purpose has been admirably achieved

In the first chapter the history of the investigations which culminated in the recognition of the relation between the islands of Langerhans and human and experimental diabetes is surveyed, along with mention of some of the early attempts to prepare active extracts of the pancreas (some of these extracts undoubtedly contained insulin), which were made prior to the successful solution of this problem by Banting and Best in 1921 After this are chapters on the preparation and purification of insulin, the chemistry of insulin as elucidated by the study of crystal-

line insulin, the standardization of insulin, modes of administration and prolongation of the action of insulin by such means as admixture with protamines, the use of insulin substitutes, duodenal extracts and guanidine derivatives and the physiologic action of insulin

The investigation of crystalline insulin, much of which has been done by Dr Jensen himself, indicates that it must be regarded as a typical protein, the composition of which does not differ markedly from that of any other protein. It represents "the first instance in which a protein possessing a specific physiological action has been obtained in crystalline form" and as such has become probably the most thoroughly investigated of all the proteins. The results of these researches indubitably connect the physiologic action of insulin with certain chemical groups in the molecule, but attempts to associate physiologic activity with a special prosthetic group, like that in hemoglobin, have failed. Several peptides containing some of the groups have been synthesized, but none of the synthetic compounds has possessed hypoglycemic activity.

To many the chapter on the physiologic action of insulin will be of most interest and importance. Here fifty-four pages of text summarize the work reported in 624 papers, which are listed in forty-five pages of bibliography. After consideration of this vast amount of material, the author takes the position that "neither the nonutilization nor the overproduction theory can completely explain the symptoms of diabetes" and that "carbohydrate metabolism is controlled by the physiological coordination of various active agents in the body." In regard to the action of insulin he says "The precise mechanism of the physiological action of insulin has yet to be fully explained."

The bibliography is well selected and there are, in addition, both author and subject indexes.

Parasitology, with Special Reference to Man and Domestic Animals By Robert Hegner, Francis M. Root, Donald L. Augustine and Clay G. Huff. Price, \$7. Pp. 812. New York: D. Appleton-Century Company, Inc., 1938.

This text is a revised edition of "Animal Parasitology" (1929) written by Hegner, Root and Augustine. The text, over 700 pages, consists of an introductory chapter on parasitism, a section of fifteen chapters on protozoology by Robert Hegner, a section of sixteen chapters on helminthology by Donald Augustine and a section of twenty-two chapters on the arthropods of parasitologic importance by the late Francis Root, revised by Clay Huff. The text has been revised for the use of students in colleges, universities, medical schools and schools of hygiene, public health and tropical medicine.

In most instances the material contained in this treatise is accurate. In an attempt to include information with regard to the less important parasites the authors have neglected the more important phases of parasitology. This is especially noticeable in the chapter on amebas. Seven pages have been devoted to the amebas of lower animals and seven pages to the methods of obtaining and preparing the parasites for study. Of the latter, six pages are devoted to the iron-hematoxylin method of staining and to the culture of amebas. Both of these procedures are too technical for the audience for whom this book is intended. The procedures for diagnosis and treatment are in instances too abstract.

Because of the broad scope of this text, with special reference to lower animals, it will probably not be used as a study guide for medical students. However, because of its voluminous bibliography and comprehensive treatment of the subject matter it is recommended as a reference for that group.

What a University President Has Learned By A. Lawrence Lowell, President Emeritus of Harvard University. Price \$1.75. Pp. vi + 150. New York: The Macmillan Company, 1938.

This book contains eight short essays which should be read by any one interested in education. Mr. Lowell's way of saying things is clearcut and positive, and what he has learned as a university president is worth reading.

Although none of Mr Lowell's discussions deal primarily with the problems of medical education, he has many wise and witty remarks about education in general that are applicable to medicine. To readers who enjoy a pungent, almost epigrammatic style the book will be a constant delight. Sentences like these are typical: "In mental as in physical instruction the question is largely one of appetite and of how this can be whetted." "Examinations like most human things are imperfect and their results are only approximate." "The choice of a career is less important than is commonly supposed. Much the same qualities are required in all professions and in all kinds of business—intelligence, good judgment, fair dealing and above all diligence with a determination to make good by work well done. Without these a man rarely succeeds in any career, with them there are an abundance of niches in almost every serious occupation."

All medical students and their teachers will find these essays stimulating.

Iodine Metabolism and Thyroid Function By A W Elmer, M D. Price \$10. Pp 605, with 23 figures and 86 tables. London: Oxford University Press, 1938.

This book is an excellent review of the subject of iodine metabolism and includes a lengthy and comprehensive bibliography in which references as recent as 1938 may be found.

After a brief historical introduction the various methods of iodine determination are presented. The remainder of the book is divided into two sections, in which are discussed the physiology and the pathology of iodine metabolism. The author not only is thoroughly conversant with the experimental and clinical research in this field but has made a number of noteworthy contributions as a result of his own investigations. He describes in detail and evaluates the experimental work dealing with the various aspects of iodine metabolism, especially as related to the thyroid gland. Disputed questions are presented impartially, and the opportunities for further investigation are indicated.

The book represents a vast amount of careful study and should be extremely valuable as a summary and reference to the biochemist and the physiologist, as well as to the clinician who is interested in fundamental problems related to the thyroid gland.

Scarlet Fever By George F Dick, M D, Professor of Medicine, University of Chicago, and Gladys U Dick, M D. Price, \$2. Pp 149, with 8 colored plates and 4 charts. Chicago: The Year Book Publishers, Inc., 1938.

This small monograph is well done. It tells the story of scarlet fever clearly and in a readable fashion. The book starts with a history of scarlet fever, chapters follow dealing with the etiology of the disease, its pathology, its clinical manifestations and its diagnosis, prognosis and treatment.

Naturally the authors have a good deal to say about cutaneous testing, susceptibility to scarlet fever, immunization against the disease and antitoxin treatment for it. The volume ends with an excellent list of references to current literature. Finally, there is a good index.

All medical students will like the book, and general practitioners, too, will find it readable if they wish to brush up on what is known of scarlet fever. The eight colored plates are good. If one were critical one might object to the two depicting the "strawberry" and the "raspberry" tongue, but, on the whole, every one realizes that the authors know scarlet fever as well as the disease can be known. It is a pleasure to have their views so clearly and simply presented.

Kaffee und Kaffein By O Eichler, M D. Price, 8.70 marks. Pp 160. Berlin: Julius Springer, 1938.

This book contains the material presented in the symposium on coffee and caffeine at the meeting of the German Pharmacologic Society in Berlin in 1938.

The original papers by W. Straub, O. Eichler and W. Stepp appeared in *Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmacologie* (190 118-170 [Sept.] 1938). Aside from the exhaustive way in which the literature in the field is presented (484 references), the chief value of the book lies in the highly critical way in which the author attempts to evaluate published and often accepted "facts" and in his presentation of unsolved problems.

The book has chapters on the history and preparation of coffee as a beverage, on the actions of coffee and caffeine on the central nervous system, circulation, kidneys, metabolism and organs of reproduction and on caffeineism and tolerance. There is an interesting discussion of the action of caffeine during muscular exercise.

This publication is timely, since the subject has—to the knowledge of the reviewer—not been presented in comprehensive form since J. Bock's article in Arthur Heffter's "Handbuch der experimentellen Pharmacologie" (Berlin: Julius Springer, 1920).

Physikalische Therapie. By H. Lampert. Price, 15 marks. Pp. 250. Dresden: Theodor Steinkopff, 1938.

This is the twenty-fifth volume of a series of monographs on various subjects for the "practicing physician." The subject of this volume is physical therapy.

The author has covered the entire field of physical treatment, which has now attained extensive proportions. Accordingly, in a 250 page monograph it is possible to include all the developments in this type of therapy in compendious form only. Whereas such a condensation obviously results in loss of certain details, nevertheless the book is of value to the general practitioner as a reference and as a means of rapidly obtaining general information concerning this type of therapy.

The rationale of the various forms of physical therapy, such as hydrotherapy, massage, exercise, application of light and of radium and electrotherapy, is discussed briefly. Their indications and techniques are described. The book is profusely illustrated with charts, diagrams and photographs. A complete index, in which the prominent subjects are printed in bold type, is helpful. A more complete bibliography would increase the value of the book as a reference.

Le duodenum, atlas de radiologie clinique. By P. Cottenot, Max Levy and E. Cherigie. Price, 285 francs. Paris, France: Gaston Doin & Cie, 1938.

This study of the duodenum, presented in atlas form, includes all of the diagnostic problems, frequent and rare, which the clinical roentgenologist may encounter in his daily practice. The roentgenograms shown are supplemented by self-explanatory diagrams, ample text and, in some instances, case histories. Adequate attention is given variations of the normal duodenal picture, anomalies, changes engendered by extraduodenal pathologic conditions, changes resulting from pressure of neighboring structures, diverticula, stenosis, duodenitis, tumor, ulcer and postoperative conditions of the duodenum.

The occurrence of definite clinical manifestations attributable to diverticula is contrary to general experience. Functional conditions, although they are discussed in relation to other topics, are not given a separate chapter, which their importance, in my opinion, justifies.

This work should be of definite practical value to roentgenologists.

PERIARTERITIS NODOSA

REPORT OF A CASE

REGINALD FITZ, M D

HARRY PARKS, M D

AND

CHARLES F BRANCH, M D

BOSTON

Periarteritis nodosa is a baffling disease. Many clinicians agree with Kussmaul and Maier¹ that its prognosis too often is obvious long before its diagnosis can be established.

A voluminous literature describing periarteritis nodosa has accumulated since Kussmaul's day, so bulky a literature, in fact, that to report another case seems scarcely excusable. We have had occasion, however, to study a patient with periarteritis nodosa during twenty months of almost continuous hospitalization and (through many friends who saw her) to develop a record of her case which we believe gives a fairly complete account of the evolution of the disorder in this particular instance from early in its course until the end. The entire affair was peculiar enough to be interesting. Some of the observations made do not appear to have been reported in other cases on record. Finally, any light that can be shed on periarteritis nodosa may prove helpful to future patients.

REPORT OF CASE

M. K., an attendant nurse, was 37 years old at the time of her death. She felt perfectly well until September 1928, eleven years before her illness terminated. After riding in the wind one day she noted a paralysis of the right facial nerve. She could not remember how incapacitating this was, later, as she recalled the episode, she remembered the development of a sensation of quivering and stiffness of the muscles of her face without any particular weakness of the muscles of mastication or expression and a continued sensation as though every movement of her face were under a skin which had been freshly sunburned.

From the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine.

1. Kussmaul, A., and Maier, R. Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsches Arch. f. klin. Med.* **1** 484-518 (Feb.) 1866.

In 1929 this sensation spread to involve the other side of her face. Persons, however, would laugh at her when she said she had "facial paralysis," for the expression of her face seemed natural, and there was no obvious muscular weakness or atrophy.

In 1931 she began to notice what she termed a quivering feeling in her legs at night when she lay down. She could not find a comfortable position for her legs. There was no actual pain but a jerkiness of the small muscle bundles.

In the fall of 1934 she noticed that her legs were quickly fatigued and began to ache when she climbed stairs and that her feet felt numb and unreal. Presently her legs began actually to hurt when she used them, to swell and to show red spots when she stood up much. Finally, for no reason that she knew, she began to have bouts of diarrhea. These were painless and consisted in the passage of about three normal-looking stools each day.

There was no tuberculosis in the family. She had never been seriously ill. After graduating from high school she worked as a clerk in a factory office. She had a course of training in the Emerson Hospital in Concord, Mass., and since 1933 had been doing private nursing almost constantly.

It may be significant that in 1926 and again in 1929 she had an attack of tonsillitis. Both attacks were severe, with each there were fever, malaise, prostration and about a week's illness in bed followed by a week's convalescence before she felt like going back to work. There was no more evident relation than this, however, between the tonsillitis, the "facial paralysis" and the muscular weakness and soreness of which she complained.

Three other points are worthy of comment. For several years she had noticed that her eyes failed to accommodate promptly. If she glanced at a near object after looking at a distant object there would be a few seconds of blurring until accommodation occurred. This difficulty was not corrected by glasses. It bothered her because she herself had noticed the development of this peculiarity and she wondered what it meant.

She had had good teeth, but since 1933 they had been too soft, her dentist told her that something was wrong with her metabolism and that this made her teeth unduly susceptible to decay.

Finally, since 1933, or for about a year before she came under medical supervision, she had been plagued by an irritating, tickling type of chronic cough. It reminded her of whooping cough without the whoop, and cough as she would, she could raise nothing. She had painted her throat, had tried various "cough medicines," all without benefit, and on the whole had found nothing helpful.

It was with a story as indefinite as this that M. K. consulted Dr. Richard Stetson of Boston in November 1934. She was worried about the way she felt, about her cough and about the manner in which her legs misbehaved, she wondered how serious an illness she had and whether it would become increasingly incapacitating.

Physical examination at that time revealed no abnormality except in the nervous system. The pupils were irregular and fixed to light. There was lateral nystagmus. The tongue deviated to the left. The arm jerks were exaggerated, the right being livelier than the left. The abdominal reflexes were absent, as were the ankle and knee jerks. There was no Babinski sign. Sensations of position and vibration in the feet were poor, and there was a definitely positive Romberg sign. There was hypesthesia of the stocking type over the lower parts of both legs. Disturbances in sensation were much more notable than were motor disturbances.

Thereafter the disease followed a zigzag course. The patient was studied from time to time in various hospitals, and it is interesting to realize how varied were the opinions offered as to diagnosis (table 1). These reflect fairly well what happened to the patient subjectively.

At first the clinical picture was that of an ill defined, diffuse disease of the nervous system, not following any definite rule and seemingly better classified as possible multiple sclerosis than anything else. Presently, however, there developed a beefy red tongue, with this there occurred intermittent attacks of diarrhea, the conditions being superimposed on what looked more and more like peripheral neuritis. Thus the question of avitaminosis and nontropical sprue arose. In 1934 bouts of fever began to occur, and at times a transitory cutaneous rash would appear. The cutaneous lesions were variously described as erythema, as urticarial wheals, as papules which made one think of insect bites or even as frankly purpuric spots. In the fall of 1936 the patient was observed at the Peter Bent

TABLE 1—*Diagnoses Suggested at Various Hospitals in the Case of a Patient with Early Periarthritis Nodosa*

Hospital 1 November 1934	Hospital 2 March 1935	Hospital 3 June 1935	Hospital 4 July 1935	Hospital 5 February 1936	Hospital 6 November 1936
? Multiple sclerosis	? Multiple sclerosis	? Multiple sclerosis	Multiple neuritis (cause undetermined)	? Nontropical sprue	Erythro melalgia
	? Nontropical sprue		?? Syphilis of the central nervous system	? Avitaminosis	? Raynaud's disease
	? Avitaminosis				? Thromboangiitis obliterans
					? Multiple neuritis (cause undetermined)
Treatment					
Antisprue diet, liver extract, high vitamin diet	Fever therapy	Antisyphilitic therapy	Antisprue diet, liver extract, high vitamin diet, tonsillectomy	High caloric diet, high vitamin diet	

Bingham Hospital. Dr. H. A. Christian, of all who saw her, came nearest to making the correct diagnosis. He believed that all her difficulties were probably on the basis of a vascular disturbance. He thought that she gave a fairly consistent history of intermittent claudication and that the redness of the feet of which she then complained was not unlike that described by Wen Mitchell as erythromelalgia. It was his opinion that the neuritic manifestations were secondary to some form of vascular disease.

The intermittent nature of the disease, with certain definite exacerbations and remissions, is well illustrated by the patient's weight chart during the course of her illness. On the whole, the remissions were of short duration and by no means complete. The course of the disease appeared slowly progressive. The prognosis was obvious many months before the diagnosis was established.

The patient entered the Robert Dawson Evans Memorial on March 15, 1937, and stayed there almost continuously until her death, in November 1938. It was not until January 1938, or ten months after her entry, that the diagnosis of periarthritis nodosa was established. The manner in which this came about is of some interest.

In the Robert Dawson Evans Memorial, as elsewhere, a great many diagnoses were suggested. The clinical picture was striking enough, the patient had peripheral neuritis, intermittent bouts of fever with abdominal cramps and diarrhea, cutaneous lesions that came and went and a beefy red tongue. Yet for a long time no one had sufficient clinical imagination to correlate all these findings logically under the definition of one disease.

In August Dr. T. J. C. Von Storch suggested that the patient might have hypertrophic interstitial neuritis and that a bit of the peroneal nerve be excised for biopsy. When this was done, the neuropathologists who were consulted agreed that the excised nerve did not show changes characteristic enough to substantiate the diagnosis.

The patient was badly discouraged. She seemed to be making no headway and was ready to try anything. She had been examined repeatedly in the hunt for possible foci of infection. Since the shadow of the gallbladder was not visualized after intravenous injection of dye, Dr. Howard Clute agreed to abdominal exploration in the hope that removal of a possible focus of infection such as a diseased gallbladder, might be followed by a remission such as had

TABLE 2—*Weight Curve in Periaenteritis Nodosa, Illustrating the Relapsing Nature of the Disease*

Date	Weight, kg
1933	71
1934	63
1935	49
Tonsillectomy	
1936	61
1937	61
1938	47
1938	36
Cholecystectomy	
1938	46

occurred earlier, after tonsillectomy. On entering the peritoneal cavity he discovered a gallbladder with many stones in it, which he removed, he also performed incidental appendectomy. He described the stomach and the upper part of the duodenum as seemingly edematous and containing multiple areas of hemorrhage throughout and the transverse and descending colon and cecum as diffusely injected and slightly thickened. The significance of these findings was not realized at the time.

Comment—In retrospect two unrelated episodes stand out as being pertinent to the case. Not long ago one of us attended a clinical-pathologic conference at the Massachusetts General Hospital. Dr. J. H. Means remarked, as the record of a patient whom he had seen in life was discussed by one of the younger clinicians, how much easier it often is to make brilliant diagnoses from a "paper case" than in reality. This certainly was true in the case of M. K. As one reads the record it seems peculiarly stupid in the light of the correct diagnosis that four years should have been necessary to establish it. In clinical medicine, as in other things, hindsight is often better than foresight.

For twenty-five years Dr H A Christian has repeated over and over to his interns and residents that in order to remain keen and with sharpened wits they must read old medical literature, current medical literature and all other kinds of medical literature. The wisdom of this advice also is well illustrated by the case of M K.

In January 1938 a review on periarteritis nodosa was submitted to the Editorial Board of the *Archives of Internal Medicine* by Dr Linn J Boyd of New York. Thus one of us was presented, so to speak, with the diagnosis of M K's disease in a neatly labeled package, for as Dr Boyd's review was studied it was obvious that the diagnosis of periarteritis nodosa fitted M K's story perfectly. The gallbladder, appendix and peripheral nerve sections were reexamined, each showed characteristic lesions of periarteritis nodosa, and thus the proper diagnosis was finally determined. During the patient's subsequent stay in the Robert Dawson Evans Memorial she went downhill gradually and

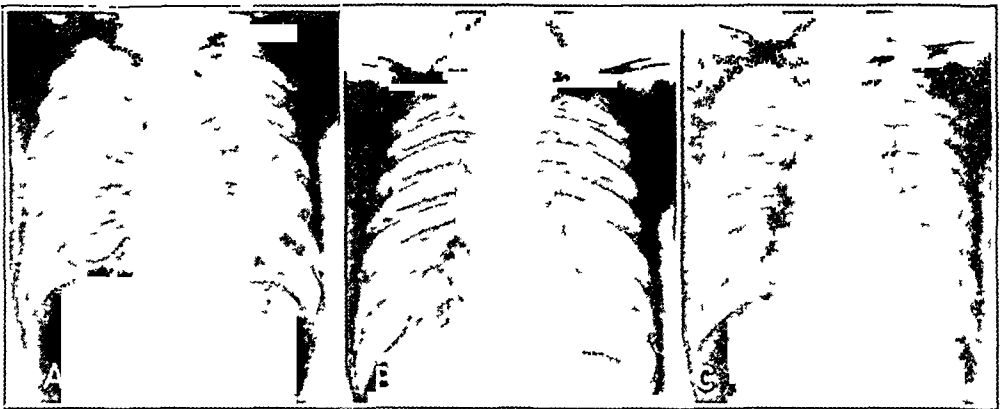


Fig 1—Increase in transverse diameter of the heart shadow. A, roentgenogram taken in November 1936. The aorta was 4.7 cm in diameter, and the width of the heart was 10.6 cm. B, roentgenogram taken in November 1937. The aorta was 5.5 cm in diameter, and the width of the heart was 11 cm. C, roentgenogram taken in November 1938. The aorta measured 5.5 cm in diameter, the width of the heart was 16.2 cm, and the heart weighed 460 Gm.

at last died. A variety of bacteriologic studies carried out in an attempt to discover some cause for the disease gave entirely negative results.

At necropsy the most striking single feature was the fact that in almost every section of every tissue examined one could observe periarterial lesions at all stages of their development: early degenerative lesions, acute inflammatory lesions and chronic or healed perivascular infiltrations around small blood vessels. The initial inflammatory lesion appeared to be acute, with neutrophilic infiltration. This was followed by infiltration of lymphocytes or eosinophils and eventually by the development of dense fibrous perivascular scarring. Apparently the process would begin in one small artery, run its course, develop in a neighboring vessel and run its course, and whatever caused the disease obeyed no set rules or regulations. Thus it was that the patient presented manifestations of a peculiar, slowly pro-

gressive and at times intermittent disease in practically every system of the body, strikingly in the circulatory system, the renal system, the gastrointestinal tract, the nervous system, the hematopoietic system and the skin

Clinically the heart sounds always were normal so far as signs of valvular disease were concerned and their quality was not abnormal. The cardiac rate, as in Kussmaul and Maier's case, tended persistently to be rapid. As time went on the heart enlarged to a surprising degree, and despite the fact that the heart muscle was diseased signs of congestive failure or of pain in the heart did not develop, nor did striking electrocardiographic changes occur.

The almost spectacular manner in which the cardiac shadow enlarged is well illustrated by roentgen measurements. Until January 1938 there was little change. But from then on something occurred to make the heart shadow increase in size rapidly, as manifested by a progressive change in transverse diameter from 12 cm. in January to 16.2 cm. in November.

Electrocardiographically all that happened at first to suggest heart disease were transitory changes in the T wave in lead I, this wave would become almost

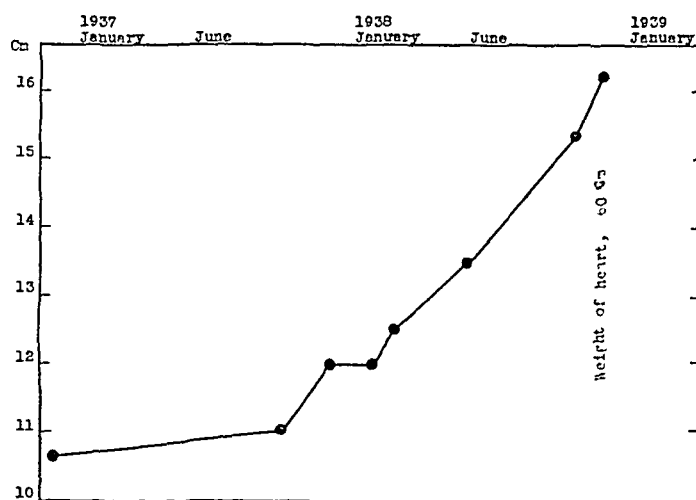


Fig 2—Graphic representation of the progressive increase in the diameter of the heart shadow as measured roentgenographically

isoelectric for a time, later to revert to its normal shape. Even three weeks before death, when a notable change in the state of the heart had occurred, the tracing still was essentially normal. The last tracing, taken shortly before death, showed clearcut abnormalities in the T wave and in the S-T segments.

That no significant congestive failure occurred is shown by the fact that in February 1938 the venous pressure was 55 cm. of water and in November, three weeks before death, it was 82 cm. of water. In August the vital capacity was 2,800 cc., and in November, 2,200 cc. There never was orthopnea. On the whole, despite the fact that organically the patient had advanced disease of the heart muscle, she had little to show for this in the way of symptoms or signs.

The heart weighed 460 Gm. The myocardium throughout was firm, dense and fibrous, cutting with difficulty. Scattered through it were numerous irregular areas of dense gray fibrous scar tissue averaging 2 to 3 mm. in diameter and having a shotty feel due to areas of old perivascular infiltration. The larger coronary branches, however, showed no irregular beading or distinct morphologic change, and their interior was smooth and glistening. The valves were normal.

Histologically, surface sections through various portions of the heart showed varying degrees of organizing pericarditis. The mesothelial cells were for the most part intact, but at occasional points the pericardium was roughened by torn fibrous adhesions consisting of rather highly vascular old connective tissue infiltrated with and containing small clumps of lymphocytes and plasma cells. Elsewhere the pericardium presented small areas of contracture in which the many newly formed capillaries were markedly engorged and the edematous, relatively recently formed connective tissue was heavily infiltrated with lymphocytes, plasma cells and monocytes, many of the last-mentioned cells containing hemosiderin. There were also occasional eosinophils. The larger coronary branches in the pericardium showed varying degrees of endothelial thickening of their intimas and fibrosis of their walls, particularly in the region of the adventitia. On pro-

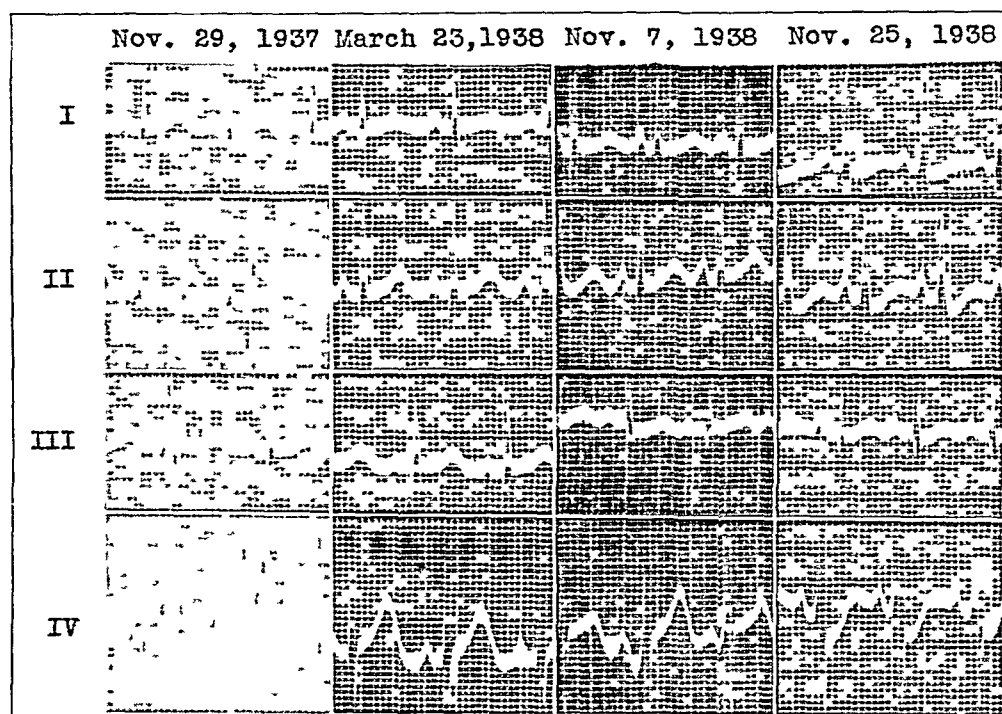


Fig 3—Electrocardiographic changes during the course of periarteritis nodosa

gressing through the myocardium extensive areas of old fibrous scars and a few small areas of more recently formed ischemic necrosis were encountered. The connective tissue throughout was edematous and infiltrated with small numbers of lymphocytes and endothelial cells. Nothing resembling Aschoff bodies was seen. The smaller arterioles showed a varying picture. In places their lumens were practically obliterated by endothelial hyperplasia of the intima, fibrosis of the media and profound fibrosis of the adventitia. About such vessels were rare lymphocytes. Rare small arterioles were present showing alternative degenerative changes. In these the intima was lined with fibrin, the endothelium was edematous and there was a necrotizing process of the media and adventitia and surrounding edema. There was no cellular infiltration. The aorta showed a fibrous and hyaline thickening of its intima, beneath which were small deposits of atheromatous material. Its media was intact and showed no histopathologic change in the

sections at hand. Its vasa vasora, however, showed granulating and healed arteriolar lesions. In none of the blood vessels examined were any aneurysms observed grossly or microscopically.

The blood pressure behaved surprisingly. Little by little it tended to become elevated, but there was a cyclic course to its curve, as though whatever caused hypertension would do so in bouts and suggesting that when the stimulus to hypertension was relieved the blood pressure reverted to normal.



Fig. 4—Healed lesion of periarteritis nodosa from the interventricular septum near the apex of the heart, showing extreme scarring of the entire wall and fragmentation of the elastica, with little regeneration, and proliferation of the intima. Only rare acute lesions were observed in the heart. \times about 177.

That the kidneys had much to do with the level of the blood pressure and the eventual development of persistent hypertension is suggested by the changes that developed in these organs.

The combined weight of the kidneys was 260 Gm. On section, the surface of each was irregularly pitted, the intervening nodular areas standing up as pale pinkish or yellowish gray zones averaging 5 mm in diameter. The normal

relation between the pyramids and the cortex was distorted though reasonably well preserved. At the upper pole of the right kidney was a small area having all the characteristics of a single infarct. The capsule was firmly adherent. The pelvis showed somewhat thickened epithelium, and the ureter was thickened and dilated. The renal arteries and veins were thickened but showed no atheromatous plaques or marked narrowing of their lumens. The large artery as it entered the hilus was fully two-thirds obliterated by dense fibrous thickening of its intima, which had in places torn or made irregular the underlying internal elastic membrane. About this vessel there was also considerable perivascular scarring.

Sections through various portions of the kidney showed varied pathologic change. All four phases of vascular lesions were present, and the pathologic picture of the adjacent parenchymatous units was directly predicated on the type

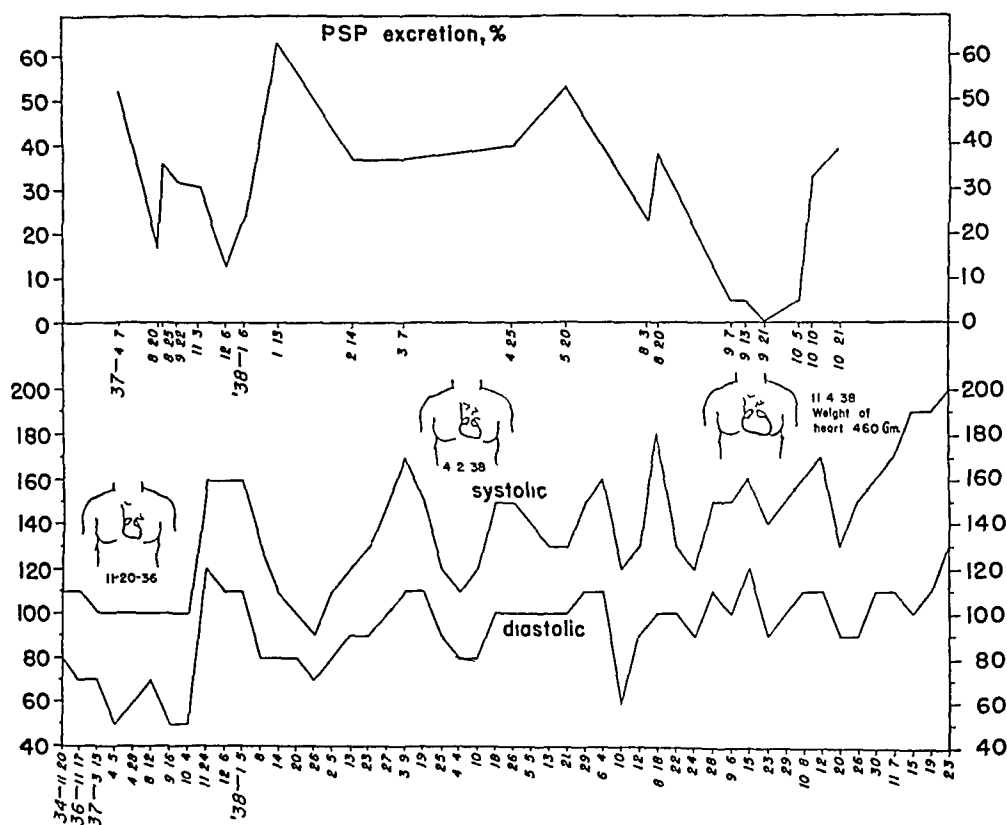


Fig 5—Varying phenolsulfonphthalein excretion and blood pressure curve during the course of periarteritis nodosa

of vascular lesion with which it was associated. The old healed lesions obviously created areas of dense scarring similar to healed infarcts; the acute lesions caused acute glomerulitis or acute interstitial nephritis with destruction of the included tubules. In little involved areas the tubular epithelium was swollen, stained faintly acidophilically and showed various stages of karyolysis and karyorrhexis. The collecting tubules almost uniformly contained hyaline or granular casts and not infrequently blood casts. Many seemingly intact and functional glomeruli were present. Others showed some capsular proliferation or fibrous thickening of the glomerular tufts. In general the efferent and afferent arterioles were intact, but where they were involved in necrotizing arteriolitis the glomerulus showed a picture either of acute hemorrhagic glomerulitis or of profound neutrophilic infiltration.

Clinically this peculiar renal lesion appeared to be characterized by exacerbations and remissions of transitory attacks of acute nephritis. The urine from time to time contained varying degrees of albumin, and a few red or white cells would appear in the sediment. There never was any increase in the nonprotein nitrogen content of the blood. Renal function, however, as judged by the excretion of phenolsulfonphthalein, varied tremendously. Presumably, had the process kept up long enough, terminal renal insufficiency would eventually have developed.

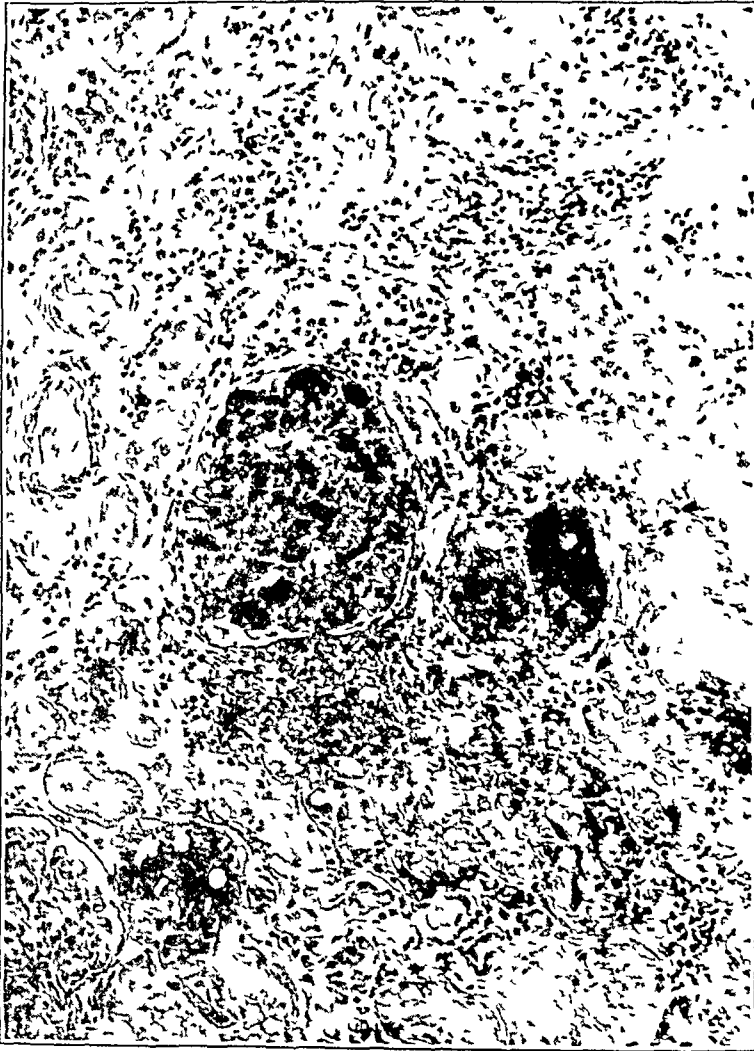


Fig 6—Section of the kidney, showing focal glomerulitis resulting from acute periarteritis nodosa involving the afferent arteriole. Note the uninvolved glomerulus near by. Both kidneys showed numerous early, advanced and healed lesions of the smaller arterioles, with concomitant involvement of the affected parenchyma. The main artery at the hilus was reduced by healed lesions to one-third its normal size.
× 144

In this particular instance, however, between the attacks of what amounted to acute nephritis due to the vascular disease enough normal renal tissue was left to maintain good renal function.

The increased capillary resistance resulting from periarteritis of the smaller renal vessels was probably an important factor in the development of hypertension. Possibly the intermittent nature of the hypertension was due to patchy destruction of the renal cortex. This causation is in line with Goldblatt's experiments.

The intestinal lesions were striking. Clinically, as has been stated, the patient complained of intermittent attacks of pain and diarrhea. These attacks might or might not be accompanied by fever. Repeated roentgen examination of the gastrointestinal tract revealed no evidence of intrinsic pathologic change. The stools never contained anything abnormal and for the most part gave no evidence of loss of blood, occasionally a moderately positive reaction to a benzidine test would be reported. That the patient was able to absorb ordinary foods was apparent because, as the weight curve revealed, she gained weight after tonsillectomy in 1936 and after cholecystectomy in 1938. While she was under observation,

TABLE 3—*Behavior of Gastric Hydrochloric Acid*

Date	Cc of Tenth Normal Acid per 100 Cc of Gastric Juice			
	Fasting	Minutes After Alcohol Meal		
		15	30	45
July 31, 1935	29	88	80	60
April 6, 1937	41	41	46	75
Aug 18, 1937	15	10	34	34
June 2, 1938	0	0	13	29

TABLE 4—*Sugar Tolerance Tests*

Date	Blood Sugar, Mg per 100 Cc				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
April 13, 1937	76	138	161	99	120
Sept 4, 1938	91	153	211	181	142

however, there developed a diminution in the ability of the stomach to excrete free hydrochloric acid in response to an alcohol test meal, the dextrose tolerance appeared to diminish and she continually lacked vitamin C.

The behavior of the gastric hydrochloric acid is shown in table 3.

Two dextrose tolerance tests were completed, one in April 1937 and one in September 1938. The results were so unlike as to be worth mentioning.

The concentration of ascorbic acid in the blood always was below 1 mg per hundred cubic centimeters, and in September 1938 a saturation test carried out according to the technic of Wright, Lilienfeld and MacLenathen² revealed only 46 per cent excretion, in contrast to a normal value of about 90 per cent.

The protein metabolism appeared to remain normal. The nonprotein nitrogen content of the blood did not become abnormally low, and, more important still, the plasma proteins showed relatively little change. To be sure, there was a slight falling off in the albumin content of the plasma, but never enough to cause reversal of the albumin-globulin ratio or a critical fall in the total protein level.

² Wright, I. S., Lilienfeld, A., and MacLenathen, E. Determination of Vitamin C Saturation, *Arch Int Med* 60:264-271 (Aug) 1937.

The data given in table 5 appeared to us of considerable interest. One gets the impression that the patient could not store vitamin C, although she was able to absorb proteins and sugar normally. We attempted to determine whether she was able to absorb fat normally by employing 500 cc of 20 per cent cream as a test meal and estimating the cholesterol and fat concentration of the plasma at later intervals. Unfortunately some of the fat meal was vomited, so that the results of the test are not wholly convincing. However, the figures are reported for what they may be worth. One gets the impression that some of the fat, at least, was normally absorbed. Why was it that in an intestine capable of absorbing protein, fat and sugar comparatively well, vitamin C seemingly should have been absorbed with difficulty?

The appearance of the intestinal tract was striking. It is remarkable that so few symptoms developed in the presence of so extensive a lesion.

TABLE 5—*Level of Plasma Protein in Grams Per Hundred Cubic Centimeters*

Date	Total Protein	Albumin	Globulin
April 12, 1937	6.4	4.7	1.7
Nov. 29, 1937	7.6	4.6	3.0
April 5, 1938	7.7	4.9	2.8
June 10, 1938	7.5	5.1	2.4
Aug. 19, 1938	7.1	3.9	3.2
Oct. 21, 1938	6.2	3.5	2.7

TABLE 6—*Fat Tolerance Test,* Oct. 3, 1938*

	Blood Cholesterol, Mg per 100 Cc	Total Fat Content of Blood, Mg per 100 Cc
Fasting	141	
2 hours	165	442
4 hours	171	
6 hours	133	842
8 hours	162	

* Five hundred cubic centimeters of 20 per cent dextrose was given by mouth.

The rugae of the stomach were poorly defined. Near the pylorus were two minute patches, each approximately 1 cm in diameter, over which the mucosa was flattened. Beginning with the duodenum and extending through the small intestine and the entire colon was thickening of the intestinal wall by edema. The mucosa presented hundreds of ulcerative lesions in all stages of formation. The early lesions averaged about 1 cm in diameter, were round and were no more thickened than was the surrounding mucosa. The next most advanced lesions were oval and circumferentially arranged, almost but not quite encircling the intestine. These lesions averaged 2.5 cm in length and 1.5 cm in width and were eroded, over them the serosa was thickened, telangiectatic and not infrequently roughened by wisps of yellow fibrin. The most extensive lesions were an accentuation of this process. Sometimes the advanced ulcers measured 4.5 cm in length and 2 cm in width. They showed no heaping up or induration of their edges. They had irregular nodular bases. They were limited peripherally by a broad zone of necrotic mucosa, and the entire intestinal wall and the overlying peritoneum were involved in the lesions. Yet there was no evidence of perforation or near perforation in any of these areas.

Sections through the esophagus and the cardiac end of the stomach showed marked submucosal edema throughout. Although the esophagus was grossly normal, it showed foci of necrosis of the surface epithelium, beneath which there was definite infiltration of lymphocytes, eosinophils and rare monocytes. The blood and lymphatic vessels were distended. The arterioles of this section, particularly in the region of the serosa, showed definite early degenerative changes. The adjacent (cardiac) end of the stomach showed massive coagulation necrosis, the mucosa, submucosa and muscularis being only faintly outlined. Extensive acute arterial lesions were present, varying from edema, swelling and necrosis of the wall to massive neutrophilic infiltration. Areas of frank necrosis of the muscularis were present, heavily infiltrated with neutrophils, particularly in the periarterial region, about such areas the capillaries were markedly engorged.

Section throughout the small and large intestine corresponded more or less identically with the gross anatomic findings. The early mucosal lesions were associated with early arterial lesions, while the more advanced mucosal lesions and frank erosions were associated with definite areas of acute arteritis. Many of the larger mesenteric arterioles were partially occluded by recently formed fibrin thrombi. Their media and adventitia were edematous, contained fibrin and were heavily infiltrated with neutrophils, eosinophils, endothelial cells and lymphocytes. There were surrounding capillary engorgement and definite proliferation of capillaries and fibroblasts. Over such vessels the adjacent peritoneum showed well defined localized peritonitis. Only rare arterioles showed any evidence of completely healed lesions.

Sections through the pancreas were interesting. For the most part the acini and islands were perfectly intact and presented a normal histologic appearance. There was, perhaps, a slight ingrowth of fat cells. Examination of the arterioles disclosed all four phases of the lesion associated with the disease at hand, acute arteriolitis predominating. One of the larger arterioles present, fully 1 mm in diameter, was completely occluded by an organizing fibrin thrombus. Half of the wall showed practically no histopathologic change, while the other half was in an advanced state of organizing acute arteritis, with fibrin, neutrophils and endothelial cells prominently displayed. Healed lesions were rare in the sections at hand, only two vessels being materially affected. These, however, presented only minute, pinpoint lumens, the remainder being replaced by dense fibrous thickening of the intima with some scarring of the media and marked scarring of the adventitia.

The liver weighed 1,910 Gm. It was soft and boggy, but the normal lobulations were well defined. The capsule was not thickened. The cut surface showed normal lobulations sharply accentuated beneath a light yellowish brown background, and this was distinctly friable and contained irregularly mottled yellowish gray areas suggesting patches of necrosis. Histologically the picture was diffuse and varied. In general, the sinusoids, particularly about the central veins, were distended with red cells, and occasional pericentral areas of replacement fibrosis suggested the terminal reaction to chronic passive congestion of some duration. At numerous points throughout the parenchyma were minute areas of focal necrosis in which the liver cells showed varying degrees of degeneration and neutrophilic infiltration.

Examination of the periportal connective tissue showed that considerable and relatively uniform damage had been occurring for some time in this zone. There were many healed arteriolar lesions with considerable surrounding fibrosis, which in places had impinged on the bile ducts, causing frank capillary bile stasis. At least two of the vessels in the section examined showed well defined

granulating lesions with virtually complete obliteration of their lumens by endothelial cells, fibroblasts and newly formed capillaries. Other vessels showed early lesions with edema, endothelial thickening, early deposits of fibrin and necrosis of their walls. There was only one vessel which showed really acute arteriolitis.

The neurologic findings were difficult to evaluate, they were notably bizarre, diffuse and inconstant. At no time were there any mental symptoms.

Historically, the first symptoms began as paresthesias involving the face. In 1934, more than four years before death, the pupils were fixed and irregular, the

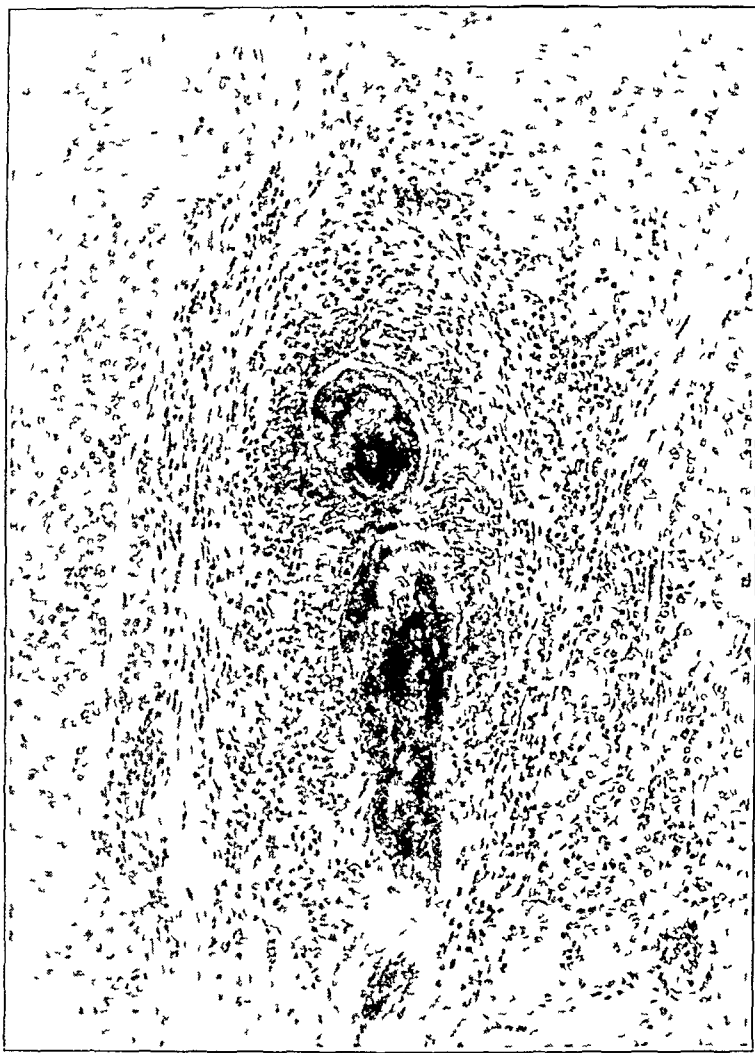


Fig 7—Section of the pancreas, showing acute periarteritis nodosa with thrombosis, edema, fibrinous exudate and heavy infiltration of neutrophils, lymphocytes and rare eosinophils. Note spilling of the process into the adjacent parenchyma. $\times 147$

tongue was deviated to the left, the right biceps jerk was greater than the left, and the abdominal reflexes, the knee jerks and the ankle jerks were absent. A little more than a year later, a weakness of the right facial nerve developed, and now there also was a readily apparent stocking distribution of hypesthesia and hypalgesia, complicated by bilateral foot drop, by atrophy of the leg and foot muscles, and by weakness of the leg muscles.

After tonsillectomy all this was followed by several months' remission. During this time the patient felt better than for a long time, she gained in strength and complained only of occasional pain in her feet.

In the fall of 1936 a second relapse occurred. In the spring of 1937, when the patient first was examined in the Robert Dawson Evans Memorial, the neurologic picture was that of extensive polyneuritis. There was peripheral loss of sensation to pain, temperature and touch on the inner aspects of the arms and below the level of the middle part of the legs. There was a small area on the upper anterior surface of the left thigh where sensation to touch alone was lost. There was marked atrophy of the muscles of the hands and feet. There was partial foot drop. The brachial reflexes were diminished, and the reflexes in the legs were absent. No fibrillary twitchings were observed. Sweating on the right side of the face and scalp at times was pronounced.

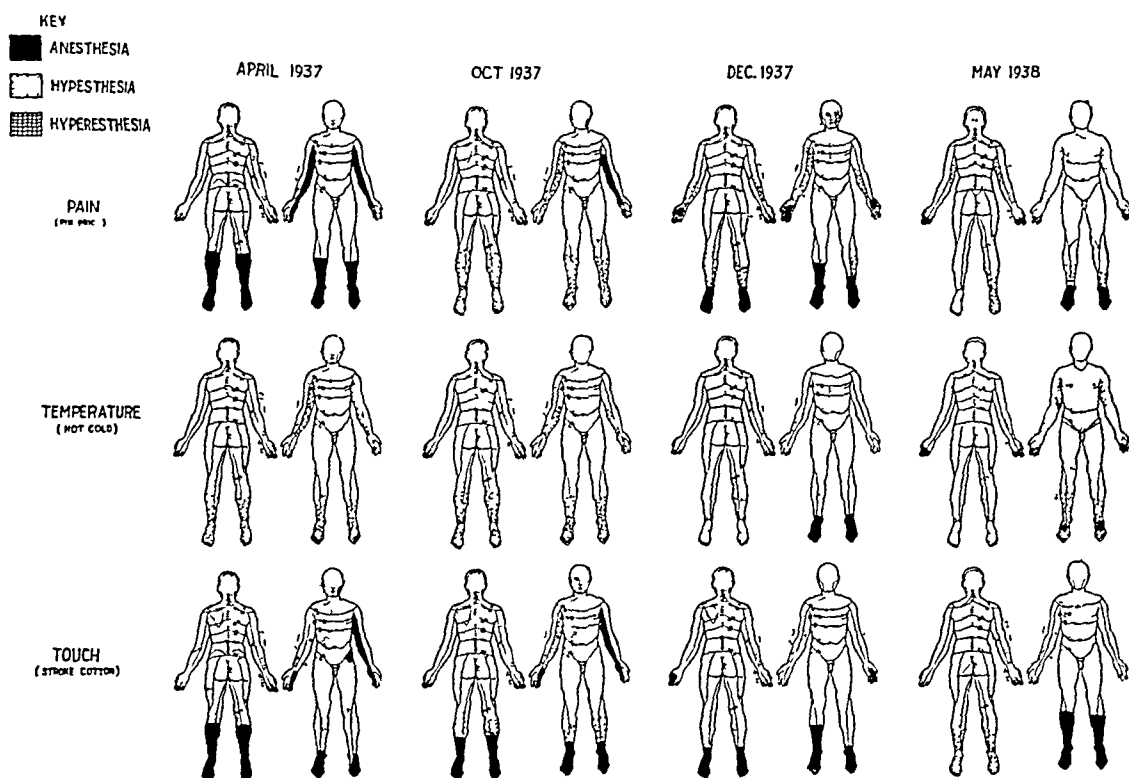


Fig 8—Varying sensory changes observed during the course of periarteritis nodosa

The pupils still were irregular, the left being larger than the right, and there still was weakness of the right facial nerve. As time went on the peripheral signs varied considerably, atrophy of the truncal muscles as well as of those of the extremities took place. Relapses and remissions of sensation (fig 8) along the peripheral nerves occurred, in all probability as new nutrient arteries to nerves were involved and went through the pathologic cycle described in other vascular areas.

Toward the end there developed transient diplopia, the optic disks, which hitherto had been normal, became choked, and a massive retinal hemorrhage appeared in the right fundus.

Throughout the course of the illness the spinal fluid showed little change. Perhaps there was a tendency for the protein to increase as the disease progressed and for the colloidal gold curve to shift to the left.

At necropsy the brain was not examined, but the spinal cord and various peripheral nerves were studied. Grossly the cord appeared normal except for a well defined engorgement of the vessels throughout. Histologically the arterioles both within and without the parenchyma of the cord were involved in healed and organizing lesions. The peripheral nerves showed the same process. The fine arterioles traversing the nerve bundles were involved in inflammatory processes. In places they showed early arteriolitis, in other places, acute or healed arteriolitis. Not infrequently the acute inflammatory process seemed to extend through the nerve sheath and to some extent to involve adjacent fibers.

The effect of the disease on the hemopoietic system was striking. In 1935, three years before her death, the patient had moderate secondary anemia with a value for hemoglobin of about 60 per cent and a red blood cell count of 4,000,000 per cubic millimeter. During her stay in this hospital the hemoglobin level ranged between 60 and 80 per cent, the red cell count remaining fixed in the neighborhood of 4,000,000. Liver, iron and transfusions made no difference. There appeared to be persistent low grade anemia which responded to no form of therapy. The sedimentation rate remained increased. The white blood cell count,

TABLE 7—*Spinal Fluid Findings*

Date	Protein, Mg per 100 Cc	Colloidal Gold Curve
Nov 19, 1934	25	0 0 0 0 0 0 0 0 0
July 31, 1935	20	1 1 1 1 0 0 0 0 0
April 12, 1937	20	1 1 2 2 2 2 1 0 0
Oct 23, 1938	42	2 2 3 2 2 1 0 0 0

on the other hand, varied from day to day, as might have been expected from all the acute lesions that existed from time to time. It ranged from 7,000 to 22,000 per cubic millimeter. When leukocytosis appeared there was regularly an increase in the proportion of polymorphonuclear leukocytes. We were unable to detect any marked eosinophilia, such as has been described in other cases. Occasionally 3 or 4 per cent of eosinophils was encountered. No abnormal forms of white cells were ever seen.

Grossly, the bone marrow appeared normal. On histologic examination sections from the marrow of the femur, vertebra and sternum all showed arterioles having marked fibrous thickening and representing a healed lesion. They also presented smaller arterioles showing early lesions, endothelial thickening and arteriolar necrosis, as well as minute arterioles showing acute lesions about which the bone marrow predominately was infiltrated with neutrophils and eosinophils.

The spleen weighed only 120 Gm and appeared normal. In spite of its relatively normal size and gross appearance, however, it showed marked histopathologic change in its arterioles. In general the capsule and pulp were not remarkable. The germinal centers were well defined and showed none of the phenomena customarily associated with acute or toxic splenitis. The arterioles showed a variety of changes. Some showed well defined edema of the intima with protrusion of the endothelium and necrosis of the remainder of the wall. Others showed marked acute arteritis, the lumen being filled with organizing blood and the wall being edematous and massively infiltrated with neutrophils, some fibrin, occasional eosinophils, monocytes and plasma cells. This infiltration

extended through the adventitia into the surrounding pulp, where foci of true acute splentitis were formed. In such areas eosinophils were frequent. Still other vessels presented well defined zones of organization, the intimal and medial thickening being definitely replaced by granulation tissue. Still other vessels were in a completely healed stage of dense general fibrosis with almost total obliteration of the lumens. Sections of lymph nodes from various portions of the body presented vascular lesions identical with those observed in the spleen.



Fig 9—Segment from the lower thoracic portion of the cord, showing acute periarteritis nodosa of an arteriole of the posterior horn, with an adjacent branch not involved except for perivascular cuffing with lymphocytes. Acute and healed lesions were noted throughout various levels of the cord, with surprisingly little pathologic change in the parenchyma. \times about 228

The cutaneous changes were varied. As early as 1934 (four years before death) there developed erythematous lesions on both feet followed by pigmentation. In 1937, after cholecystectomy, the skin over the abdomen and the lower parts of the legs acquired a peculiar blotchy appearance, and the skin over the incision took months to heal. Early in 1938 the face and neck became pigmented. A few

months later urticaria-like lesions over the trunk developed from time to time. Finally, during the last few months there appeared on the forearm tender, evanescent pulsating nodules surrounded by areas of erythema or purpura.

At necropsy a characteristic cutaneous lesion was removed. Immediately below the left antecubital fossa the skin presented an irregular nodular elevation approximately 1.5 by 4 mm. The underlying tissue was distinctly injected. The surface epithelium was intact, and the immediately adjacent corium showed little histo-

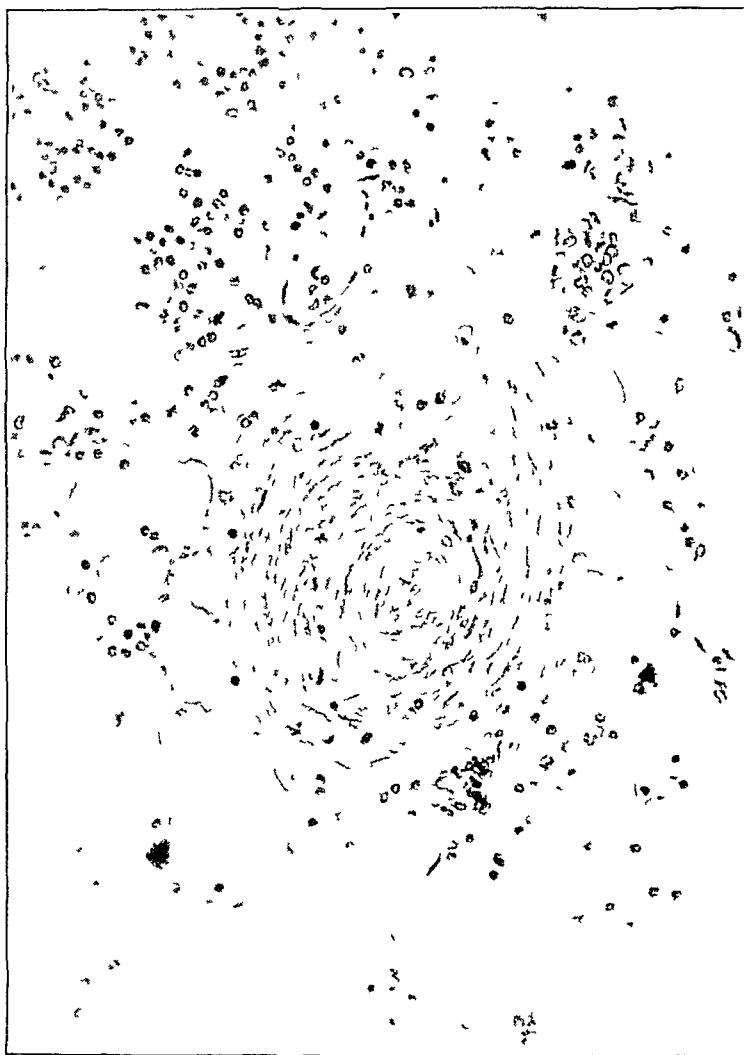


Fig. 10—Femoral bone marrow, showing the early stage of periarteritis nodosa with endothelial proliferation, edema of the wall and neutrophilic infiltration. Sections from sternal, vertebral and femoral marrow all showed early and healed lesions. $\times 238$

pathologic change. The fibrofatty tissue, however, contained arterioles in which early, acute and healed lesions were observed.

One puzzling clinical finding was the manner in which the basal metabolic rate behaved. It tended to be elevated, but in an intermittent fashion. There were no other signs of hyperthyroidism, and the basal metabolic rate was never con-

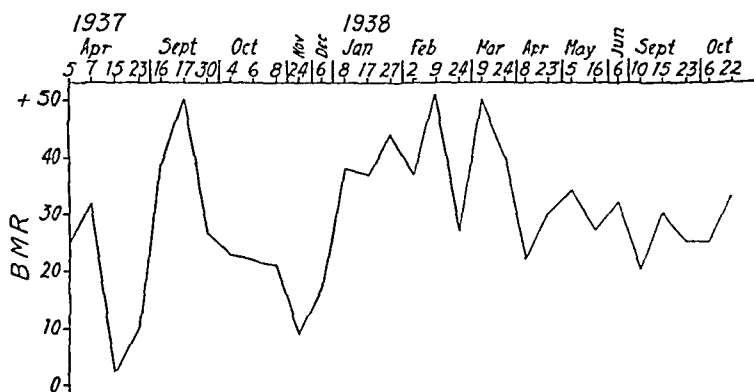


Fig 11—Varying basal metabolic rate during the course of the disease

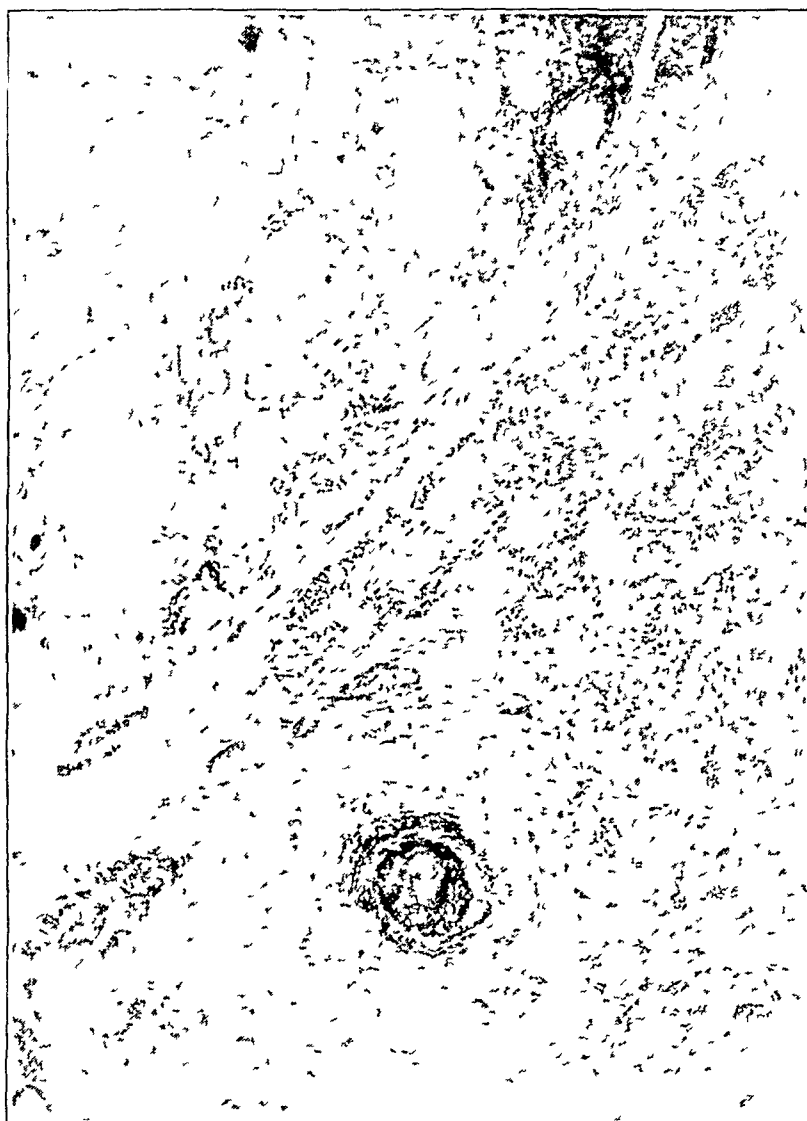


Fig 12—Section of the thyroid in a case of acute periarteritis nodosa, showing numerous old and recent lesions, all of which involved the adjacent parenchyma to some extent $\times 735$

sistently influenced by iodine. The trend of the metabolic rate was as eccentric as the blood pressure level and the renal function.

Neither the thyroid nor the adrenal glands appeared grossly remarkable, yet each showed periarterial lesions.

Sections through the thyroid showed the acini to be relatively uniform in size and shape, filled with normally staining colloid material and exhibiting no evidence of secondary hyperplasia. Careful examination of its stroma, however, revealed numerous vessels affected by the disease process. Occasional vessels showed profound fibrosis and a healed stage. The most extensive lesions, however, were acute, in these the arterioles were partially to completely occluded by fibrin thrombi, their edematous walls being infiltrated with fibrin, many neutrophils, some endothelial cells, lymphocytes and rare eosinophils. There was definite capillary proliferation about the periphery of such vessels. One or two of the arterioles presented a striking picture, one side being entirely normal while the other half was massively involved in profound acute arteriolitis.

The vessels about the periphery of the adrenal glands also showed acute arteriolitis with fibrin thrombi, edema and fibrin deposits in the wall and infiltration with neutrophils, lymphocytes, endothelial cells and (rare) eosinophils. Similar lesions were occasionally seen in the vessels of the medulla. About these areas there were small foci of necrosis.

In 1933, it will be remembered, the patient complained of an irritating, non-productive cough which lasted for a long time. During the months that she was under our observation, however, cough was never an important symptom. Thus, clinically the pulmonary system was the one system in which there was no sign of pathologic activity. From this point of view the pathologic description of the lungs is especially significant.

The lungs together weighed 1,020 Gm. Grossly they showed no significant change. The great vessels were normal. On histologic study the bronchi showed no specific inflammatory processes. Careful examination of numerous vessels throughout showed well defined, healed arteriolar lesions in the form of dense medial and adventitial fibrosis. At no point in the sections observed were we able to see any acute or organizing arteriolitis. A few of the larger arterioles showed edema of the intima with swelling and protrusion of the endothelium. There was also edema of the media and adventitia. The remainder of the lung showed little evidence of pathologic change beyond the accumulation of albuminous coagulum within the aveoli.

COMMENT

This case is reported as of especial interest because the patient was under careful observation for so long a time. All our findings are typical, they bring out little new.

Certainly the history of periarteritis nodosa disposes to clinical humility. In the seventy-three years which have elapsed since Kussmaul and Maier described the case of Carl Seufalth, little that is significantly new has been added to the general knowledge of the disease. Kussmaul and Maier deserve full credit for recognizing a new clinical syndrome, a clinical picture which, as they said, became the more perplexing the longer it was observed and with a prognosis likely to be evident long before the diagnosis could be established.

Even with the old-fashioned and crude methods of histologic study at their disposal, they gave an adequate description of the nodular thickening which they found so characteristically around countless small arteries in their case, and they believed that the disease commenced acutely in the media of these small arteries, all other clinical and pathologic manifestations being secondary to this fundamental lesion.

In our case the pathologic observations well confirmed the clinical findings. The intermittent, prolonged course of the illness and all its symptoms can be explained by the peculiar jumble of acute, subacute and chronic or healed vascular lesions which were seen in nearly every tissue examined.

Kussmaul and Maier were no less humble than we when it came to saying what might cause such a disease. Since their time many theories have been put forward. No one, however, has succeeded any better than

XXIII

Ueber eine bisher nicht beschriebene eigenthümliche Arterien-
erkrankung (Periarteritis nodosa), die mit Morbus Brightii
und rapid fortschreitender allgemeiner Muskellähmung
einhergeht.

Von

Prof. A. Kussmaul und R. Maier

in Freiburg i. Br.

Hierzu Taf. III—V

Krankengeschichte

Carl Seufarth von Gernsbach, 27 J. alt, Schneidergeselle, kam 4. Mai
1865 Morgens 10 Uhr in die medicinische Klinik zu Freiburg. An dem ziemlich
mageren Menschen fiel die ungemein blasse Farbe von Haut, Lippen, Mund-

Fig. 13.—Title of a paper published in 1866 and containing the first description of periarteritis nodosa.

they in determining the nature of the agent which injures so remarkably the smaller vessels of various organs and which causes such an extraordinary clinical picture. Until the causative agent is found, little can be said of treatment.

It is interesting that Kussmaul and Maier drew attention to the fact that certain patients with periarteritis nodosa may recover spontaneously. They saw Landolin Faust, who fell sick in August 1864 with an illness much like Carl Seufarth's. Faust, however, grew better and recovered to some extent. In August 1865, biopsy of a bit of muscle was done, and this showed periarterial lesions comparable with the lesions observed in the case of Seufarth. Kussmaul and Maier recorded this experience and warned against the possible danger of biopsy in such cases, the wound from this minor operation required eight weeks for complete

healing, a situation comparable to that is our case, in which the gall-bladder incision failed to heal completely for many months. Nowadays, too, the disease need not be entirely hopeless, and occasionally the patient may recover. This is illustrated by the case of C W P, a patient whose medical adventures Dr Albert R Paikhurst of Beverly, Mass, has been kind enough to summarize for us and allow us to report.

C W P was 39 years old in 1932 when he first entered the Beverly Hospital. His history was uneventful except that for a little over a year he had been bothered by asthma. His sinuses and antrums contained polyps, which were duly treated. General physical examination otherwise gave negative results. It was noted that on one occasion on his first admission to the hospital the white blood cell count was 17,000 per cubic millimeter, with 7 per cent eosinophils.

In 1933, about a year later, he suddenly had a violent headache with pain under both shoulders and a stiff neck. He reentered the hospital and was found to have normal blood pressure, normal physical findings except for asthmatic rales in both sides of the chest, a strongly positive Kernig sign, discrete glands palpable in the neck, axillas and groins, a choked disk on the left side and grossly bloody spinal fluid under greatly increased pressure. He was hospitalized for a month, growing better with repeated spinal punctures. During this time the white blood cell count ranged between 12,000 and 15,000 per cubic millimeter, there was no eosinophilia. The urine varied in gravity and occasionally contained albumin and a few red or white cells in the sediment.

In 1934 he again felt ill and reentered the hospital. For several months after leaving he had been comfortable and fairly active, but by degrees his legs became stiff, his feet began to ache, and finally a peculiar variety of cutaneous lesions developed. The cutaneous lesions were variously described as being of five types: hemorrhagic, nodular, bullous, urticarial and eczematous. The nodules were largest on the forehead, with smaller areas over the back of the hands and the dorsa of the feet. Accompanying the nodules were enlarged glands in the axillas and in the groins. His pain was striking. Even at rest his feet were extremely painful, and the pain appeared to be deep seated rather than superficial. On this admission to the hospital there were inexplicable bouts of crampy abdominal pain with or without diarrhea, and areas of anesthesia and hyperesthesia were noted over the upper parts of both legs. He remained in the hospital for several weeks, occasionally he had slight fever, the white blood cell count ranged between 18,000 and 45,000 per cubic millimeter. Usually the predominant leukocytes were polymorphonuclear, although on one occasion 50 per cent eosinophils were noted, the urine was normal except for an occasional trace of albumin and for rare red cells and granular casts in the sediment, there was no hypertension, and the Wassermann reaction was repeatedly negative.

One of the subcutaneous nodules and at least one of the nasal polypi which had been removed from time to time revealed vascular lesions consistent with the diagnosis of periarteritis nodosa.

The patient gradually grew better and six years later was entirely well except for asthma. There had been no recurrence of cutaneous lesions, of cerebral symptoms, of leg cramp or of abdominal pain. About all that was appreciably left of his illness was slight weakness and hyperesthesia of the left hand and left thigh and hands and feet which felt the cold more easily than is normal.

He died suddenly in an asthmatic attack. Necropsy revealed a rare healed lesion around the smaller arterioles in the heart, the kidneys and the intestinal tract. On the whole, the striking feature revealed by the examination was the miraculous manner in which all active lesions of periarteritis nodosa seemingly had disappeared.

Periarteritis nodosa remains much as it was when first described. It is a freakish vascular disease of unknown origin, likely to prove fatal within a few weeks or months from the time it first causes symptoms, producing extremely varied clinical manifestations and not yet subservient to any specific form of prevention or cure.

CHRONIC MALARIA

A CLINICAL CONSIDERATION

GEORGE H FONDÉ, M D

AND

EDGAR C FONDÉ, M D

MOBILE, ALA

Malaria is a chronic disease, not alone an infection of the blood stream characterized by chills and fever. Failure to comprehend or detect its insidious course and its strong tendency to relapse, even after months or years, accounts for the fact that it still ranks as one of the serious social and economic problems. Some authors¹ have recognized the persistent and prolonged course of malaria, nearly all acknowledge it to be the most widespread and destructive of tropical diseases. Because in its chronic form it is generally disguised, the problem of control is doubly hard to master.

We are not concerned here with early "classic" forms of malaria. These conditions constitute the minority and are largely limited to well known regions, they offer little or no difficulty in diagnosis and are easily controlled, temporarily at least, by specific treatment. Moreover, in these early infections plasmodia can usually be demonstrated (except in hyperpyrexial, cerebral and "blackwater" forms)².

On the other hand, in dealing with chronic malaria the physician is confronted with a complex problem. In this stage the disease is not easy to recognize, and it is difficult to demonstrate the parasite. The chronic infection is generally masked under syndromes closely resembling a number of common local and systemic diseases. In all cases it tends to become asymptomatic, whether treated or not, during some phase of its course.

INCIDENCE

First, it should be pointed out that there are no geographic limitations to the chronic forms of malaria, as contrasted to early typical infections, which are largely confined to endemic zones. From a study of 10,000 malarial patients in the dispensaries of Odessa, U S S R, Korovitskiy³ concluded that chronic malaria does exist in temperate

1 Heiser, V. *An American Doctor's Odyssey: Adventures in Forty-Five Countries*, New York, W W Norton & Company, Inc., 1936.

2 Mackie, T T. Personal communication to the authors.

3 Korovitskiy, L K. *The Problem of Chronic Malaria*, *Vrach delo* **19** 359, 1936, abstracted, *J A M A* **104** 470 (Aug 8) 1936.

climates where reinfection is not possible. According to his data not more than 40 per cent of patients were cured at the end of four years. The greater number of cases of chronic involvement usually escape recognition, especially when removed from malarial regions. There is now reason to suspect that in this day of constant travel to and from areas of inoculation more patients with chronic malaria are to be found outside the endemic regions than among the static populations, the condition is not recognized, largely because of the mistaken impression that a change of climate alone will effect a cure. Such an infection is generally regarded as having been eradicated, despite recurrence of atypical symptoms, and the impaired health passes for injury done rather than for disease still present. Petritz,⁴ from a study of malaria in Illinois, was convinced that there were between 15,000 and 25,000 cases of chronic malaria in that state, in most of which the condition was unrecognized and untreated. If this is an index of its prevalence, what must be the total number of cases of chronic involvement unrecognized and untreated in the whole of the United States? Statistics officially published on the incidence of malaria are generally based on demonstration of parasites rather than on clinical evidence. We believe that such statistics are by no means a true indication of the extent of malaria.

CLASSIFICATION

Chronic malaria may be divided into two clinical types

1 *Reactive Chronic Malaria*—The reactive type is that in which the defensive forces are more or less vigorously operative. This type embraces a latent, an atypical and a typical late phase.

In the latent phase the progress of the disease is arrested because of the prompt destruction of parasites by a highly developed immune mechanism.⁵ Vigorous and well nourished subjects may appear to be in fair general health when reactivations have not been too frequent or persistent. Such patients are usually ambulatory. Even those whose general health is obviously impaired often refuse to believe that they are subjects of a chronic infection, because the progress of the disease has been so insidious. They rarely seek medical attention, their condition remains unrecognized, a lower level of vigor is casually regarded as an individual characteristic or idiosyncrasy, rather than the result of a chronic disease.

4 Petritz, L. J. Chronic Malaria. Some Clinical Aspects, Illinois M. J. 44: 193, 1936.

5 Taliaferro, W. H., and Cannon, P. R. The Cellular Reactions During Primary Infections and Superinfections of *Plasmodium Brasiliense* in the Panamanian Monkey, J. Infect. Dis. 59: 72, 1936.

The atypical phase, manifested in the great majority of all cases of chronic involvement, always produces definite symptoms, although these symptoms are extremely varied. The clinical manifestations depend on localization of the colonies of parasites in fixed tissues (reticulo-endothelial cells) and vary according to the extent of toxic and allergic effects as well as to individual susceptibility to them. On account of the prevailing concepts of what is required for diagnosis, malaria in this phase is often overlooked. There is sufficient phagocytic and humoral immunity to destroy circulating parasites, which accounts for the absence of typical symptoms in these patients.

The typical late phase is seen in patients who have lost their power to resist parasitic invasion of the blood stream. However, the parasites may not be demonstrable in the peripheral blood in the first few days of this phase, they are more frequently discovered at the end of twenty-four hours, after the third typical paroxysm. We have often noticed the reappearance in the blood smear of large numbers of both schizonts and gametocytes.

2 Nonreactive Chronic Malaria—In the nonreactive type the patient is extremely ill, disabled and confined to bed. The infection has advanced to a dangerous point, and the patient's defensive powers are exhausted. His body fails to react characteristically to malarial proteins released at the time of segmentation, hence the diagnosis is difficult. These are often called "quinine-fast cases"⁶. Demonstration of parasites is rarely possible, and the absence of parasites is presumed to be the result of severe toxemia. The temperature is normal or subnormal for the greater part of the time, the patient is at or near the cachectic stage, which is characterized by advanced organic degeneration, and the related symptoms frequently disguise the long-existent primary cause. Subjects in a cachectic state of chronic malaria often have a dry, copper-colored skin, which is an important diagnostic point when the history discloses early attacks occurring over a number of years. This type of malaria is commonly observed in children before the development of immunity as well as in persons enfeebled by age who have lost their relative degree of immunity.

DIAGNOSIS

A practical diagnosis of chronic malaria rests on the results of four methods of investigation, namely, taking of an exhaustive history, a complete physical examination, specific drug tests and laboratory procedures.

⁶ Pais, A. Radio-Stimulation in the Treatment of Malaria, in Contributions to Radio-Stimulative Therapy, series 1 and 2, Rome Istituto de radio-eccitamento, 1926, Radio-Stimulation in the Treatment of Malaria Radion, *ibid*, series 4, 1928

A study of the history should be directed mainly toward exclusion or confirmation of previous attacks of malaria. Exposure to inoculation and previous acute attacks would suggest the possibility of persistence and chronicity of the infection. When the evidence (previous frank attacks, positive diagnosis or previous treatment) points toward malaria, the burden of proof in differential diagnosis becomes reversed, i. e., it becomes necessary to disprove the presence of malaria before other considerations are taken up. Such a method of evaluation of the patient's status with regard to a previous infection obtains with syphilis. It should likewise be regarded as of the greatest importance with malaria, which has similar relapsing tendencies. The late H. R. Carter made the statement, "Its duration in man, if not eternal, is indefinite."⁷ Sir Ronald Ross stated that his father had typical malaria seven years after leaving the region of possible reinfection.⁸

Notation of the time at which exacerbations occur is of great assistance in recognizing the periodicity, or rhythm of recurrence, of symptoms. In early malaria the usual interval for the two tertian varieties of parasites is approximately forty-eight hours. Such a frank invasion is readily confirmed by microscopic demonstration of the parasites in all stages of incubation (exceptions already mentioned). On the other hand, the periodicity manifested in the atypical phase, as observed clinically, is seven to ten days.⁹ This regular recurrence is aptly illustrated by the ocular forms of malaria, in which the symptoms are clearcut both subjectively and objectively. As far as we can ascertain, no explanation has been offered to show why exacerbation of symptoms in atypical malaria should occur at the seven to ten day interval. It is reasonable, however, to suppose that the vegetative cycle of the parasites is delayed in the more shaded and protected lodgments as compared with the fuller exposure to the activating influence of sun and light on circulating parasites. Deaderick¹⁰ stated

Relapses at short intervals have been recognized since the time of Hippocrates. Later the "septenary" periods were noted for tendencies to show relapses, and this

7 Carter, H. R., in Maxcy, K. F. *Epidemiological Principles Affecting the Distribution of Malaria in Southern United States*, Reprint 920, United States Treasury Department, Public Health Service, 1924, p. 3.

8 Ross, R. *The Prevention of Malaria*, London, John Murray, 1910.

9 One of us (G. H. F.) recalls that the seven to ten day periodicity in afebrile chronic malaria was first brought to his attention by his preceptors. Great emphasis was placed on the pathognomonic evidence of periodic supra-orbital unilateral neuralgia in old cases of malaria. Attention was called also to the frequency of other periodic neuralgias in afebrile malaria as diagnostic and as specifically responsive to quinine.

10 Deaderick, W. H. *A Practical Study of Malaria*, Philadelphia, W. B. Saunders Company, 1909.

idea is still largely prevalent among the laity. This is also in accord with the observation of Cohen and Trielle. They state that this period is 5 to 21 days, usually 5 to 10 days, and that the relapses may consist of one or more typical malaria paroxysms, or they may be atypical.

Recent research has thrown new light on this aspect of the subject, revealing and probably removing the points of disparity between clinical knowledge of the disease and the life cycle of the parasite in human beings. The first important fact pertains to schizogony in reticuloendothelial cells. On March 18, 1937, James and Tate¹¹ demonstrated before the Royal Society of Tropical Diseases and Hygiene of Great Britain the full vegetative cycle in the endothelial cells lining the brain of the domestic fowl. This experiment was made with the avian strain of the parasite but will probably prove to be a working basis for understanding malaria in human beings. The second fact is the experimental demonstration of the latent phase of the disease. Taliaferro and Cannon in their brilliant work on primary infections and superinfections have shown that the development of phagocytic activity renders the disease asymptomatic in spite of the fact that parasites reproduce at the same rate. Their experiments were carried out with Panamanian monkeys, and *Plasmodium brasilianum*⁵ was used.

These two discoveries, we believe, are epoch making. They reaffirm and establish the importance of clinical interpretation rather than dependence on laboratory findings, which has long been emphasized. The possibility of a vegetative cycle in man and the certainty of latency will do much to correlate the knowledge of the many parts of the problem of chronic malaria into one continuous and comprehensive whole. The well recognized periodicity (forty-eight hours for tertian varieties, seventy-two hours for quartan) is subject to many alterations. When multiple infections are present or when mixed varieties of parasites coexist the clinical picture is less definite. The symptoms are related to overlapping of the respective cycles. The reproduction of parasites in fixed tissues may again modify the periodicity. The diagnosis may be facilitated if the clinician carefully determines the time relations of the earliest paroxysms. We shall mention later the employment of "specific drug tests." This early clinical behavior is especially important in the estivoautumnal variety of infection. In this type a remittent rather than an intermittent recurrence of symptoms is noted except in the first two or three paroxysms. When this tertian infection becomes pernicious, the seizures progressively anticipate by two or more hours the regular time of occurrence. The increasing virulence is further manifested by a longer duration of the attack. They are then without intermission and without frank remission. Thus, a "closing up"

¹¹ New Light on the Life-Cycle of the Malaria Parasite, editorial, *Lancet* 1 764, 1937.

of the intervals conceals the abrupt beginning time of segmentations, and the improvement noted in the intervals between early paroxysms is lacking. We have repeatedly observed this pernicious course in atypical malaria as well as in the classic forms. Such a development is generally supposed to occur with the third paroxysm, and we believe that it should be recognized in time to avert the extremely critical complications.¹²

Punctual exacerbation of symptoms is a distinctive characteristic of malaria. In the bacterial diseases the symptoms usually attain their maximum gradually toward the latter part of the day. In malaria, however, there is an abrupt onset, generally within two hours of noon. These seizures coincide with the release of malarial toxins and merozoites. Pronounced improvement in the intervals between attacks has often influenced us in favor of malaria rather than toward an abdominal disease requiring operation or some other acute disease. We have often been aided in making a diagnosis by noting the astonishing coincidence of relapse in old known cases and the influx of new ones. A wavelike prevalence of the condition is seen in the spring and fall and following extraseasonal rises in temperature.

On inspection, the subject with chronic malaria of recent activity discloses a muddy subicteric tint of the skin and scleras. The tongue is broad and coated, often showing marginal indentations made by the teeth. There is a general pallor of the mucous membranes. The spleen in all cases of chronic involvement is notably affected. The majority of patients present prolapse of the organ with definitely increased splenic tension, which is especially noted on the day after a paroxysm. Usually the spleen is palpable at or several inches below the costal margin. In order to differentiate enlargement or prolapse of the spleen from other causes, the patient should be carefully palpated on successive days, and the findings should be correlated with periodic recurrences already discussed. Abdominal examination is best accomplished when the stomach and colon are empty. Percussion is a valuable adjunct to palpation, replacing the latter for obese or muscular patients.

Specific drug tests are decidedly the most valuable methods of detecting malaria in atypical and latent phases. The provocative test consists of one day of full dosage with either quinine or atabrine (an acridine dye). Recognizable symptoms will be brought about within a few days to three weeks, especially if the test is carried out during the

12 In cases of acute involvement this clinical characteristic was often seen during the Spanish-American War. Among the Michigan and Illinois troops were many patients with febrile and "algid" comatose forms of malaria. These forms were confused with uremic coma, owing to the associated nephritis, until parasite demonstration was made in a few cases. Other patients had severe chills an hour or two before becoming unconscious.

seasons of expected reactivation. The therapeutic test consists of one full week's course of atabrine or quinine. Marked relief from symptoms and improvement of the general condition within the following week or ten days indicates probable malaria. A confirmation of the diagnosis would be made by a sharp and more characteristic return of the periodic symptoms. In the atypical phase this test is modified by administering the specific drug to cover three successive seven day cycles (according to the therapeutic program which we shall propose). The fullest response is generally noted after the fourth week, the fourth paroxysm would not appear, but marked improvement is soon observed¹³. These specific drug tests are contraindicated for patients whose vitality is extremely low.

The employment of "protein shock" and the use of epinephrine and other agents, such as hot baths, have been recommended to facilitate the demonstration of parasites in the blood. We have not found such measures effective in enabling us to find the parasite, but they are decidedly helpful in aiding clinical recognition of latent and atypical phases of chronic infection.

Every patient should have the benefit of a general examination of the blood in addition to careful and repeated search for plasmodia. The degree of anemia and injury to blood cells often reveals important evidence. The most frequent indication incriminating malaria is stippling of the red cells twenty-four hours after an attack and marked increase of eosinophils. For indications of long-standing damage from the infection, poikilocytosis and other evidence of the injured hemopoietic organs are often noticed. The Bass-Jones concentration test has yielded the greatest success in demonstrating the parasites in blood smears. We have found the reaction to be positive more frequently when the blood is taken twenty-four hours after the occurrence of the atypical symptoms. The Henri melanoflocculation test has been of aid in a smaller number of cases.

DIFFERENTIAL DIAGNOSIS

A previous history of chronic malaria with seasonal relapses is the most important consideration in diagnosis. As with syphilis, the manifestations of chronic malaria are so protean that the symptom complex of almost any disease can be simulated. Therefore, we believe it to be impractical to give here a more detailed method of differential diagnosis than has already been suggested. However, it is worth while to list some conditions with which chronic malaria may be confused or in which it may play the primary etiologic role.

¹³ Statistics recently reported (Gill, D. G., and Smith, M. Atabrine as a Malarial Prophylactic Agent. Experiment with the Drug in Central Alabama, J. M. A. Alabama 8:66, 1938) support this clinical interpretation.

TREATMENT

There is undoubtedly a need for collective treatment of persons who are unable to obtain individual clinical guidance. Without discrediting such collective methods, "standardized" procedures have dulled the judgment of clinicians in general and obscured the importance of chronic malaria in the population. We object to the prevailing system of treatment for five reasons. 1 Heavy saturating doses are employed

Table of Conditions

System	Disease	Syndromes	Symptoms
Gastrointestinal (of greatest frequency)	Cholecystitis, uncinariasis, vitamin deficiencies, sprue, typhoid fever, typhus fever, undulant fever late syphilis	Hepatitis, allergies,* Addison's disease, catarrhal jaundice, Banti's disease, amebic infection	Pain over right lobe of liver, nausea or vomiting near noon, distress and fulness about throat and neck, abdominal, focal and surgical symptoms diarrhea dysentery
Nervous system (2d in frequency)	Psychoneurosis, encephalitis	Neurasthenia, epileptiform seizures, migraine like headaches, neuralgias	Insomnia, phobias, headaches, syncope herpes simplex, herpes zoster, vertigo, globus hystericus, tremors
Circulatory blood (3d in frequency)	Blood dyscrasias, agranulocytosis,† leukemias, essential hypertension, hypotension, Raynaud's disease, purpura, symptomatic anemias	Urticaria, angioneurotic edema	Anginoid pains faintness and vertigo tachycardia
Genitourinary	Pyelitis, hemorrhagic nephritis	Hematuria, hematuria uremia and uremic coma	
Respiratory	Pneumonia, asthma	Bronchitis (recurring)	
Ocular	Unilateral glaucoma, keratitis punctata, chorioretinitis		
Bone and Muscular	The arthritides	Lumbago torticollis	Articular, muscular and osseous pains
Endocrine	Gonadal deficiency thyrotoxicosis		

* The coincidence of chronic malaria and hay fever and asthma syndromes has been noted in a large proportion of cases in children and adolescents (Fondé, G. H. *Clinical Aspects of Hay Fever and Asthma*, J. M. A. Alabama 1: 471, 1932)

† Fondé, E. C., and Fondé, G. H. *Allergy as the Direct Etiological Factor in Malignant Granulopenia. Clinical Study Based upon One Fulminant Case*, J. M. A. Alabama 3: 375, 1934

in a chronic disease. 2 Treatment is based on the idea that destruction of parasites in the circulating hemocytes removes the infection from the fixed tissues also. 3 The individual follow-up treatment of an inveterate relapsing disease is not taken into account.^{13a} 4 Employ-

13a Angus McDonald (*Malaria Problems of Today*, in Nelson's Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, vol. 7, pp. 299-345) reported that 10 grains (0.65 Gm.) of quinine daily for thirty days is followed by relapse in 30 per cent of cases within two months. He further states that while absolute removal of parasites from the blood, therefore, "a parasite cure," cannot be guaranteed thus, yet the subjugation of relapse is a matter of taking quinine, and the termination of relapse is proportionate to the period of taking quinine.

ment of these standardized systems is too frequently based only on the demonstration of parasites. Satisfactory control of the disease is not effected in a great majority of cases of chronic involvement. Therefore, we believe that there is urgent need to revise the concepts of treatment. The plan presented here, in our experience, has proved to be a far more satisfactory method of treatment than the standardized methods and is not open to the objections which have been cited.

The plan is designed to take care of certain considerations which are extremely important in the successful management of chronic malaria. The fundamental principle is to administer the specific drugs so that the maximum concentration will be present in the blood when the merozoites are released. This concept is generally adhered to but too often is inadequately carried out because the treatment is insufficiently prolonged. Neglect of this necessity is probably due to the fact that the occurrence of atypical symptoms has not been recognized as an indication for therapy. Furthermore, the appearance of symptoms may be approximately calculated in advance if careful study is made of past recurrences so that the most effective time for drug therapy can be predetermined. Such administration of specific drugs greatly aids the natural phagocytic response by diminishing the number of merozoites, thus it also prevents an excessive release of malarial proteins and degradation products, which would result in toxic and allergic shocks to the liver and other vital organs. Lastly, but of great importance, general debility of the patient and exhaustion of the hemopoietic system are prevented.¹⁴

GENERAL MEASURES

The patient should remain in bed during the febrile stage. The diet should be light during administration of large doses of quinine or atabrine. Purgation is employed to facilitate proper absorption and tolerance of these drugs, this is effectively accomplished by small doses of mild mercurous chloride and sodium bicarbonate followed by a saline purgative. Alkalinization is desirable, and for this one of the effervescent alkaline salt combinations is used. (Sinton has shown that a patient with malaria requires several times more alkaline salts to render the urine neutral than does a normal subject.) Sedation is usually required at the beginning to alleviate the discomfort and psychic disturbance caused by the specific drug.

SPECIFIC MEASURES

As the management of chronic malaria demands a prolonged plan of treatment, we prefer to employ atabrine and quinine in alternate

¹⁴ Fonde, E. C., and Fonde, G. H. Allergy as the Direct Etiological Factor in Malignant Granulopenia. Clinical Study Based upon One Fulminant Case, *J. M. A. Alabama* 3: 375, 1934.

courses provided there is no contraindication to either drug. Quinidine sulfate may in some cases be substituted for quinine if the latter is objectionable. Our experience convinces us that atabrine in general is decidedly the most effective agent and is better tolerated in effective doses than quinine. Because atabrine is more slowly eliminated it stands guard against fresh entry of merozoites into the fixed tissue cells for a longer time than does quinine, and therefore relapses are less frequent with the former drug. Atabrine also has a special virtue in infection by *Plasmodium falciparum* and in other pernicious forms of malaria. On the other hand, atabrine should not be given too frequently, on account of its cumulative effect and the discoloration which it produces in the skin.

Objection has been made to atabrine on the ground that it is sometimes responsible for inducing psychoneurotic symptoms or aggravating those already commonly present in chronic malaria. We believe that this does occur, particularly in "cerebral cases." However, it is our opinion that focal reactions in the brain are comparable to the Herxheimer effect in syphilis under specific treatment. We have long observed that after the definite aggravation of symptoms on institution of treatment there was a remission of psychic disturbances. We have been gratified to note that in general the psychoneurotic subjects who have previously been afebrile and unresponsive to treatment have had a periodic temperature curve and have improved markedly with treatment.

We have abandoned the use of plasmochin as a therapeutic agent because of its extreme toxicity (see comment on epidemiologic value).

The doses given will naturally vary somewhat with the individual case, depending on the body weight and general vitality of the patient as well as on his response to treatment.

OUTLINE OF TREATMENT

Attack Period (to abate the early paroxysms) —The following drugs and quantities may be given

Days

- | | |
|-------|-----------------------------------------------------------------------------------------------------------------|
| 1-3 | Atabrine, 1½ grains (0.09 Gm.) three times a day, or
Quinine sulfate, 10 grains (0.65 Gm.) three times a day |
| 4-5 | Rest period |
| 6-8 | Atabrine, 1½ grains (0.09 Gm.) twice a day, or
Quinine, 10 grains (0.65 Gm.) twice a day |
| 9-10 | Rest period |
| 11-12 | Atabrine, 1½ grains (0.09 Gm.) twice a day, or
Quinine, 10 grains (0.65 Gm.) twice a day |

Maintenance Period —The following drugs and quantities are correct for this period

Days

- 14-20 Rest period
- 21-23 If atabrine was employed previously, quinine sulfate, 10 grains (0.65 Gm) at midnight
If quinine was employed previously, atabrine, 1½ grains (0.09 Gm) twice a day
- 24-30 Rest period
- 31-33 Atabrine, 1½ grains (0.09 Gm) twice a day
- 34-40 Rest period
- 41-43 Quinine, 10 grains (0.65 Gm) at midnight

[NOTE —When quinine has been found objectionable, atabrine should be given in one full course at the beginning of treatment (15 tablets of 1½ grains [0.09 Gm] each) Atabrine should then be omitted for at least two weeks before the half-course (seven tablets of 1½ grains [0.09 Gm] each) is given Subsequent half-courses of atabrine should be spaced four, five, six, seven and eight weeks apart, according to the season, for reasons previously explained]

Consolidation Period —This alternating use of quinine and atabrine continues with the rest period increasing by one week up to four weeks (early spring, summer and fall months) and up to eight weeks (winter months) During rest periods injections of iron and arsenic or bismuth compounds are given These are almost as important in the treatment of chronic malaria as are the specific drugs We prefer to avoid the free use of arsenic in cases in which there is evidence of serious impairment of hepatic function We therefore employ half-courses of iron and arsenic, either intramuscularly or intravenously, in the form of cacodylate of iron, a 1 grain (0.06 Gm) ampule every four days until six are given This may be alternated with intramuscular injections of a bismuth compound, also in half-courses (six doses) at four day intervals Injections of bismuth subsalicylate in oil are started to establish tolerance to this drug The drug may be given in aqueous solution for subsequent doses, which causes less pain locally but is more rapidly eliminated If indicated, succeeding half-courses are spaced progressively further apart Liver extract is of value in hemopoiesis, thus combating anemia We wish to stress that general supportive measures and good hygiene are necessary Easily digested foods which have a high vitamin and mineral content should be prescribed In case of malaria in which there is damage to the liver, liberal quantities of warm water containing small doses of sodium phosphate (taken two hours before breakfast) stimulate better flow of bile and intestinal evacuations

NONREACTIVE MALARIA

The guiding principle in the management of nonreactive malaria is improvement of the vital condition of the patient by employment of supportive measures as previously mentioned. Specific drugs should be cautiously administered. It is important to check the leukocyte count, which should improve after the administration of quinine or atabrine. If the leukocytes are decreased the specific drugs should be withheld. They may be resumed with caution after an increase in the white cell count is noted. A very light exposure to roentgen rays is claimed to be an effectual substitute for the well known "mountain air and altitude" in its effect on the hemopoietic tissues.⁶

The necessity of repeated readjustment of the schedule of therapy should be kept in mind, these readjustments are made on the slightest evidence of reactivation. In many cases reinauguration of the "attack period" is indicated.

Experience has taught us that in most cases it is necessary to extend the treatment of malaria over a period of two to three years. As with all chronic diseases, the complete cooperation of the patient is absolutely essential for the success of the treatment. The patient should record the time at which the slightest suggestion of a return of recurrent symptoms of the same character as during previous attacks takes place. The time of new symptoms should also be recorded. We name this a "diary and calendar system." It should include the patient's schedule of treatment. All patients should be kept under close clinical supervision as long as any active evidence of the disease exists. They should be asked to report for examination with their records at progressively longer intervals.

COMMENT ON EPIDEMIOLOGY

Attention is directed to the significance of two recent reports in regard to the inadequacy of present methods of approach in preventing the spread of malaria. First, malaria in the United States, according to statistics during the past decade, shows a steady rise in the mortality rates and a greater extension in the endemic areas northward and westward from the so-called malarial zones.¹⁵ This is true notwithstanding vastly increased expenditures and more exhaustive research. Second, the Commission of the League of Nations on Malaria has reported that eradication of malaria from a community by prophylactic treatment with drugs is virtually impossible. The report goes on to say, however, that it is desirable to provide adequate and easily available

¹⁵ Faust, E. C. Malaria Mortality in Southern United States for the Year 1936, *South M J* **31** 816, 1938.

treatment for the clinical manifestations of the disease so that the morbidity, mortality and physical incapacitation of the afflicted persons may be diminished ¹⁶

We believe that the solution of the problem as applied to a community lies in thorough treatment of the individual patient. We thereby are directing our efforts toward eradication of the sources of infection (plasmodia carriers) which are so abundantly supplied by patients with the active and chronic conditions. Plasmochin in minute doses is recommended by some authorities as an efficient agent for removing the circulating gametocytes, so that infection of the mosquito is less likely to result. In cases in which there is persistence of gametocytes after the first intensive course of treatment, we have employed plasmochin, $\frac{1}{6}$ grain (0.01 Gm.) at three day intervals until plasmodia are no longer found.

Certain groups are recognized as particular hazards to malaria communities by reason of greater violence resulting when they become infected and greater numbers of gametocytes develop for mosquito transmission. We refer to the unacclimated members of the population and to children, who are thought to be prolific sources for the dissemination of malaria,¹⁶ presumably because of their relatively low degree of immunity.

It is therefore urged that the physician consider malaria in the light of public health and that the public health officials adopt a system whereby close cooperation between physician and official is assured, in order that an adequate check-up can be made on all cases of malaria.

SUMMARY

The concepts of diagnosis and treatment presented in this article are based on a study of malaria during forty-two years of active practice. Many of the same cases were under observation for periods ranging from fifteen to thirty-five years. A large percentage of the cases were of the estivoautumnal variety.

Chronic malaria is the most prevalent form of the disease, it has no strict geographic limitation, and it is largely unrecognized and untreated.

Various clinical phases of malaria are described and suggestions for their recognition are given. In this connection it is pointed out that the atypical phase is most frequently seen.

Objections to "standardized treatment" are cited, and a plan of treatment obviating these objections is presented.

Finally, comment is made on the epidemiologic value of thoroughly treating the individual patient.

¹⁶ The Treatment of Malaria, Fourth General Report of the Malaria Commission, Bull. Health Organ., League of Nations 6:897, 1937.

CONCLUSIONS

Chronic malaria is essentially a persistent infection with a strong tendency to relapse seasonally and extraseasonally in lowered states of vitality. For a practical diagnosis of chronic malaria greater dependence must be placed on the clinical history and on the clinical manifestations.

In the treatment of chronic malaria, control of virulence and arrest of progress of the infection is effected by a prolonged follow-up. Brief courses of specific drugs, spaced in accordance with the periodic releases of merozoites, to prevent breaking down of phagocytic defense by overpowering multiplication of parasites, and the employment of general measures of vital support are the principal means of controlling the disease in the individual.

Control of malaria in communities rests mainly on effective control of the volume and virulence of the malaria organisms exposed to mosquito transmission by prompt and thorough treatment of all infected persons. This method recommends itself because it is in accord with the natural laws operative against the spread of malaria as of other diseases. It would be more desirable than eradication of the infection in populations exposed to inoculation, and it would at the same time control the morbidity, the mortality and the incapacitation resulting from malaria.

BIOPHOTOMETER TEST AS INDEX OF NUTRITIONAL STATUS FOR VITAMIN A

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AND

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After the report by Jeans, Blanchard and Zentmire¹ that the biophotometer may be used to measure a subject's nutritional status for vitamin A, work was begun in this laboratory, as in many others to test its usefulness for this purpose. The present article reports the results of over 2,000 biophotometer tests of 459 subjects—194 adults and 265 children during more than a year of experimentation. These tests have been made on subjects with both good and poor diets, with and without supplements on subjects kept for long periods on diets deficient in vitamin A and on subjects with very high levels of vitamin A intake. Furthermore, the reading for subjects on the depletion diets have been correlated with the amount of vitamin A found in the blood. The purpose of the testing has been to determine first the reliability of the test and then its validity as a measure of vitamin A stores. The results of the biophotometer studies are reported in this article, those of the studies of the blood in another publication².

Since the literature on this subject has been reviewed by others, the review will not be repeated here. Suffice it to say that reports from eight additional laboratories on the use of the biophotometer have appeared. Two of these³ confirmed the findings of Jeans and his associates, three⁴ gave what may be termed qualified confirmation, and in

From the Department of Home Economics, the University of Chicago

1 Jeans, P C, Blanchard, M S, and Zentmire, Z. Dark Adaptation and Vitamin A, J A M A **108** 451-458 (Feb 6) 1937

2 Steininger, G, Roberts, L J, and Brenner, S. Effect of a Depletion Diet on the Vitamin A in the Blood of Normal Adults, J A M A, to be published

3 Jeghers, H. The Degree and Prevalence of Vitamin A Deficiency in Adults, J A M A **109** 756-762 (Sept 4) 1937. Corlette, M B, Youmans, J B, Frank, H, and Corlette, M G. Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults, Am J M Sc **195** 54-64 (Jan) 1938

4 Schuck, C, and Miller, W O. Dark Adaptation of the Eye and Vitamin A Storage in Young Adults, Arch Int Med **61** 910-915 (June) 1938. Gridgeman, N T, and Wilkinson, H. Night Blindness and Vitamin A Deficiency, Lancet

(Footnote continued on next page)

three⁵ it was stated that the biophotometer test is unreliable and of doubtful value for diagnosing vitamin A status. The evidence at present, therefore, appears to be about equally for and against the usefulness of the test. It is significant to note, however, that the two most extensive and well controlled studies—those of Palmer and Isaacs—are in the negative group. Nevertheless, one cannot ignore the positive findings of the other workers that subjects with low readings have improved on vitamin A supplementation and that in 2 subjects (1 of Jeghers' and 1 of Booher's) a diet deficient in vitamin A caused marked impairment in dark adaptation, the subsequent addition of a supplement resulting in rapid improvement. It is clear, however, that these results must be repeated in tests of larger numbers of subjects under carefully controlled conditions before the usefulness of the test in practical nutrition can be demonstrated. The present study represents a contribution to this aspect of the problem.

METHOD

The biophotometer and the technic of its use were described in full by Jeans and his associates.¹ A brief statement of the theory back of the test and the chief points of the method which are essential for an understanding of the present article will be given.

The test is based on the theory that ability to see in the dark is dependent on the presence of visual purple in the retina. When the eye is exposed to a bright light the visual purple is bleached and the visual threshold is raised. The speed and amount of regeneration of visual purple in the dark is believed to be dependent in part on the presence of an adequate amount of vitamin A.

The test is carried out in a dark room. The subject is asked to look into the machine and to state when he sees the middle dot on a screen in which the dots are arranged in the form of a quincunx. The five dots are of graded illumination, and their brightness is controlled by a rheostat. This rheostat is connected with a dial, the divisions of which represent the logarithms of the intensity of light expressed as "milli-

1.905-907 (April 16) 1938. Booher, L. E. Vitamin A Requirements and Practical Recommendations for Vitamin A Intake, *J. A. M. A.* **110**:1920-1925 (June 4) 1938. Booher, L. E., and Williams, D. E. A Study of the Biophotometer as a Means of Measuring the Vitamin A Status of Human Beings, *J. Nutrition* **16** 343-354 (Oct.) 1938.

5 (a) Palmer, C. E., and Blumberg, H. E. The Use of Dark Adaptation Technique in the Measurement of Vitamin A Deficiency in Children, *Pub. Health Rep.* **52** 1403-1419 (Oct. 8) 1937. (b) Palmer, C. E. The Dark Adaptation Test for Vitamin A, *Am. J. Pub. Health* **28**:309-319 (March) 1938. (c) Snelling, C. E. The Biophotometer as a Test for Vitamin A Deficiency, *J. Pediat.* **13** 506-509 (Oct.) 1938. (d) Isaacs, B., Junge, F. T., and Ivy, A. C. Vitamin A Deficiency and Dark Adaptation, *J. A. M. A.* **111** 777-780 (Aug. 27) 1938.

foot-candles" Thus, in each reading taken the amount of light required by the subject to see the middle dot of the quincunx is recorded

The testing period of twenty-three minutes is divided into three parts (1) a ten minute period in the dark, during which readings are taken to familiarize the subject with the testing procedure (the fore-period), (2) a three minute exposure of the subjects' eyes to a bright light for the purpose of bleaching the visual purple (the bleaching period), and (3) a second ten minute period in the dark, during which visual purple is regenerated (the recovery period) During the recovery period four readings are taken at three minute intervals, the first of which is taken approximately twenty-five seconds after the bleaching light has been turned off In interpreting the findings Jeans stated that the shape of the curve for the entire test should be considered but indicated that the two most significant readings are (1) the one taken immediately after the light is turned off and (2) the one at the end of the test

In the present study a standard procedure was used in testing All of the timing for the test was done with a stop watch Special care was taken to expose the subject's eyes to the bright light for exactly three minutes and to insure that he kept his eyes open and looked directly at the light during the bleaching period In analyzing the data the two readings indicated by Jeans as most significant were used, namely, the one taken immediately after the bleaching period and the last one in the test For the sake of brevity these will be referred to hereafter as the "first" and "last" readings To avoid confusion the entire series of eight readings taken during the twenty-three minute period will be termed a "test," the individual observations being designated as "readings"

The data obtained are reported in dial readings rather than in "milli-foot-candles" of light The reasons for this were explained fully by both Palmer^{5a} and Isaacs^{5d} and will not be reviewed here In order to facilitate comparison with the standards suggested by Jeans and his co-workers and with the work of other laboratories, the "milli-foot-candle" equivalents for some of the dial spaces of the instrument used, as furnished by the manufacturers of the biophotometer, are given in table 1 The limits of the normal, borderline and subnormal zones suggested by Jeans are also included

RELIABILITY OF THE BIOPHOTOMETER TEST

The first step in attacking any problem of research is to determine the reliability of the test to be used for measuring results, that is, the degree to which the findings can be reproduced by the same operator on the same subjects under standard conditions In the case of the Birch-Hirschfeld photometer, work never proceeded beyond this stage,

because of inability to secure reliable readings. In the present study the data used in determining the reliability of the biophotometer test were obtained from 6 adults who were given from sixteen to twenty tests each, 50 children given six tests each and 283 subjects—48 adults and 235 children—who were given two or three tests each. Space does not permit presentation of the details of the methods used, but the essential findings may be summarized as follows:

1. The readings for individual subjects vary considerably from test to test even under standard conditions. This variation may be sufficient to change the classification of the subject from the normal to the borderline or the subnormal zone (by the Jeans standards) or the reverse. It is obvious, therefore, that single tests of a subject are of no value for diagnostic purposes.

TABLE 1—*Milli-Foot-Candles of Light Equivalent to the Dial Spaces for the Biophotometer Used in This Study*

Dial Spaces	"Milli-foot Candles"	Zone Represented by First Reading in Recovery Period	Dial Spaces	"Milli-foot Candles"	Zone Represented by Last Reading in Recovery Period
5	3.41	Subnormal	40	0.136	Subnormal
10	2.15	Subnormal	43	0.103	Upper limit of subnormal
15	1.36	Subnormal	45	0.0855	Borderline
18	1.03	Upper limit of subnormal	50	0.054	Upper limit of borderline
20	0.855	Borderline	55	0.034	Normal
23	0.650	Upper limit of borderline	60	0.0215	Normal
25	0.540	Normal	65	0.0136	Normal
30	0.341	Normal	70	0.0085	Normal

2. The first test of a child is the least reliable single test as judged by the self-correlation technic. The second test, however, is as reliable as any of the subsequent single tests. It is suggested, therefore, that in working with children the first test should be considered only a practice test.

3. Although the results of individual tests vary, the direction is as often up as down, so that the trend for an individual subject is fairly uniform. The test may be considered fairly reliable, therefore, if the trend of a subject's readings over an appreciable period is used both for establishing a base line in the control period and for determining the level with an experimental regimen.

4. The mean readings in repeated tests of groups of subjects are fairly stable; they show no consistent tendency either to improve or to regress on successive tests. This is due to the fact that the random variations of individual subjects tend to balance each other in the total group. Thus, the learning factor reported by Palmer was not observed.

in this study. It follows, therefore, that the effect of an experimental procedure may be measured by the change in mean readings, provided (a) that large enough groups are used, (b) that the study is adequately controlled and (c) that the significance of the differences obtained is determined by accepted procedures.

5. A study of other factors that might affect the test showed that the time of the day the test was taken, the time in relation to meals and the operator giving the test had no significant effect on the readings obtained. The age of the subject, however, did have an appreciable effect on biophotometer readings. Adults over 30 years of age with an optimal intake of vitamin A had significantly poorer dark adaptation than did children or young adults. If, therefore, the test is to be used, different standards should be used for older subjects.

This preliminary work demonstrated that the biophotometer test is only fairly reliable and that its use should be safeguarded by the aforementioned considerations.

VALIDITY OF THE BIOPHOTOMETER TEST AS A MEASURE OF VITAMIN A STORES

The degree to which the test can be duplicated under standard conditions having been determined, the crucial problem of its validity can be considered, that is, whether the results of the test are in reality an index of the subject's nutritional status in respect to vitamin A. This problem was subjected to three types of attack: (1) a comparison of the biophotometer readings of subjects from high and of those from low socioeconomic groups; (2) the effect of vitamin A supplementation on the readings of subjects with low levels of the vitamin as compared with those of a matched group; and (3) the effect of a long period of depletion of vitamin A and subsequent supplementation on the biophotometer readings.

COMPARISON OF BIOPHOTOMETER READINGS OF SUBJECTS OF HIGH AND THOSE OF LOW SOCIOECONOMIC STATUS

If the biophotometer test is a valid measure of vitamin A stores there should be a significant difference in the readings for subjects with good and those with poor dietary histories. To check this point, two groups of children representing the two extremes of socioeconomic status were compared (100 children from the University Laboratory School and 160 children from two of the poorest sections of the city). Comparisons were made on two bases: (1) the mean biophotometer readings for the groups and (2) the percentage of children in each group whose readings classed them as normal, borderline and subnormal. It

is seen in tables 2 and 3 that by both methods of comparison the children from the better socioeconomic group had a definitely higher status than those from the less favored groups. The mean biophotometer readings for the 100 children from the laboratory school were 22.8 dial spaces for the first and 62.6 for the last reading in the recovery period, those for the 160 children in the poorer group, 19.7 and 55.8 respectively for the same readings. The differences between these readings for the two groups were eight times the probable error and therefore are statistically significant. By the second method of analysis, moreover (table 3), it was seen that 26 per cent of the university group were classed as "normal" by the Jeans standards and only 21 per cent as definitely sub-

TABLE 2—*Means and Standard Deviations of the First and Last Readings in the Recovery Period of Children from a High and a Low Socioeconomic Group*

Classification of Subjects	Number of Subjects	First Reading in Recovery Period		Last Reading in Recovery Period	
		Mean Dial Reading	Standard Deviation	Mean Dial Reading	Standard Deviation
High socioeconomic group	100	22.8	4.21	62.6	10.21
Low socioeconomic group	160	19.7	4.43	55.8	8.65

TABLE 3—*Percentage of Children from the High and Low Socioeconomic Group Classified as Normal, Borderline or Subnormal According to the Jeans Standard*

Subjects	Number	Normal, Percentage	Borderline, Percentage	Subnormal, Percentage
High socioeconomic group	100	26.0	53.0	21.0
Low socioeconomic group	160	15.6	41.9	42.5

normal, as compared with 15.6 per cent of the poorer group who fell in the "normal" and 42 per cent in the "subnormal" zone.

These comparisons tend to support the validity of the test, since the group that presumably had the better stores of vitamin A also gave the higher biophotometer readings. Acceptance of validity on this basis, however, makes it necessary to explain the fact that 74 per cent of the superior group fell in the borderline and subnormal zones. It is recognized, of course, that the diets in this group may not all have been optimal in vitamin A, but it is difficult to believe that so large a number were deficient. An alternative explanation would be that the diets of the majority of these children were in reality adequate and that the standards of Jeans are too high. This possibility is supported by the finding that the mean readings for the 46 children in the university group who had been taking vitamin A concentrates were no higher than those for the rest of the group.

EFFECT OF A VITAMIN A SUPPLEMENT ON
BIOPHOTOMETER READINGS

The second approach was to determine whether subjects with subnormal readings could be made to improve by a vitamin A supplement. The children from the poorer locality were used to check this point. From the original 160 children who were given tests, two groups of 50 each were formed by pairing children on the basis of age, height, weight, intelligence quotient and original biophotometer readings. Although individual pairs could not be perfectly matched on every item, care was taken not to match a child who was much underweight with one over average or one with a low intelligence quotient with one with a high quotient and to give the odds on the different items first to one group and then to the other. As a result, two groups were formed whose means for every item used in matching were almost identical and whose individual pairs were remarkably alike in significant factors. These groups were considered well adapted for the study.

After a second test, therefore, each child in the experimental group was given a supplement of vitamin A in the form of carotene for five days a week during a period of eight weeks⁶. For the first six weeks this daily supplement was 10,000 units, during the last two weeks it was increased to 20,000 units per day. Each child was given his capsule of carotene individually and was required to swallow it in the presence of the observer. At two week intervals biophotometer tests were given all the children in both the control and the experimental groups, making a total of six tests of each child. It should be noted that this study differs from those reported in the literature in the size of the group studied and in the facts that the controls and the experimental subjects were carefully matched at the beginning of the investigation and the progress of each child was observed by regular tests throughout the study.

The effect of the supplement was judged by comparing the progress made by the two groups on the basis of (1) the mean readings, (2) the percentage of children in normal and subnormal zones and (3) the relative improvement made by partners in the matched pairs.

Mean Biophotometer Readings—When the mean biophotometer readings for the two groups in each of the six tests are compared (table 4, chart 1) it is seen that there was little difference in their progress. The experimental group did, it is true, show a net increase in the mean readings of 1.5 dial spaces for the first reading in the recovery period, while the control group showed a decrease of 0.8 dial spaces. When, however, the trend for the means of the individual tests is observed (chart 1), it is seen that this difference was contributed

6 The carotene was supplied by the S. M. A. Corporation, Cleveland.

largely by the last two tests and may easily have been fortuitous. The same trend was noticed in the last readings in the recovery period, the experimental group was slightly in the lead but not significantly so. If, however, each of the two groups is subdivided into the subjects for whom the highest, the intermediate and the lowest original test values were recorded, it is found that most of the improvement was made by the group for which the levels were lowest. The means for the first reading for the 16 controls and the 16 experimental subjects in this lowest group, identical at the beginning, diverged widely on succeeding tests and were 4 dial spaces apart on the sixth test (chart 1). That this improvement of subjects with low levels of vitamin A was not due to the "centripetal" drift observed by Isaacs and his associates^{5d} is evidenced by the fact that the matched partners in the control group did not show a significant improvement.

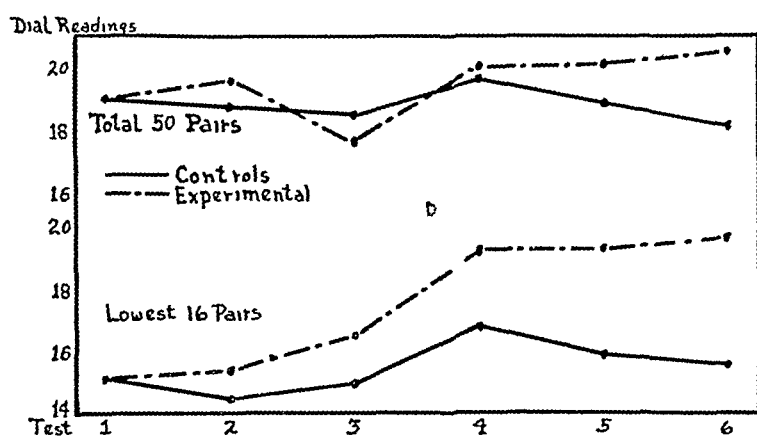


Chart 1—Comparison of the mean readings for the control and for the experimental group in each test

TABLE 4—Mean Dial Readings of Each Group of 50 Children in Each of the Six Tests

	Total (50 Pairs)		Lowest (16 Pairs)		Middle (18 Pairs)		Highest (16 Pairs)	
	Con trol	Experi mental	Con trol	Experi mental	Con trol	Experi mental	Con trol	Experi mental
First reading in recovery period								
First test	18.9	19.0	15.1	15.1	18.8	19.5	22.6	22.4
Second test	18.7	19.6	14.5	15.4	19.6	18.8	21.8	21.6
Third test	18.5	17.6	15.0	16.5	19.8	16.8	20.4	19.8
Fourth test	19.6	20.0	16.8	19.3	19.3	18.8	22.8	22.2
Fifth test	18.9	20.1	15.9	19.3	19.2	18.8	21.4	22.2
Sixth test	18.1	20.5	15.6	19.6	17.6	19.4	21.1	22.8
Last reading in recovery period								
First test	56.1	55.0	54.1	50.1	55.0	55.6	59.3	58.6
Second test	57.1	53.7	53.9	49.1	55.6	54.9	61.9	56.9
Third test	55.3	53.6	53.6	52.5	54.8	52.3	57.4	56.1
Fourth test	56.3	55.2	54.9	53.5	55.3	52.6	58.8	59.8
Fifth test	55.3	56.3	53.4	55.4	53.9	55.5	58.7	58.1
Sixth test	52.8	55.6	51.8	54.8	52.1	54.2	54.9	58.1

Change in Percentage of Children in Normal and in Subnormal Zones

—An advantage for the experimental group is also shown by the change in the number of subjects whose readings classed them as "normal" or "subnormal" by the Jeans standards at the beginning and end of the study (table 5). The percentage of normal subjects in the experimental group increased from 8 to 20, while in the control group it remained unchanged. Conversely, the percentage of the experimental subjects rated as definitely subnormal decreased from 50 to 32, while that of the control group increased from 44 to 56. It is again noted that the greatest part of the improvement was contributed by the 16 children for whom the lowest original readings were recorded.

TABLE 5—*Percentage of Children in Each Group Classified as Normal, Borderline and Subnormal at the Beginning and End of the Study*

Group	Normal		Borderline		Subnormal	
	Control	Experimental	Control	Experimental	Control	Experimental
Total (50 pairs)						
Second test	8 0	8 0	48 0	42 0	44 0	50 0
Last test	8 0	20 0	36 0	48 0	56 0	32 0
Lowest (16 pairs)						
Second test	0 0	0 0	12 5	6 2	87 5	93 8
Last test	6 2	6 2	12 5	56 3	81 3	37 5
Middle (18 pairs)						
Second test	5 6	0 0	50 0	55 6	44 4	44 4
Last test	0 0	16 6	38 9	38 9	61 1	44 5
Highest (16 pairs)						
Second test	18 7	25 0	81 3	62 5	0 0	12 5
Last test	18 7	37 5	56 3	50 0	25 0	12 5

Relative Progress of Partners in Matched Groups—The most severe as well as the most reliable method of assessing the results is to compare the relative progress of the individual partners in the 50 matched pairs. To facilitate such a comparison chart 2 has been prepared. It shows the first dial reading in the recovery period for each of the 50 matched pairs in each of the six tests. It is evident at a glance that there is great variability in the readings from test to test, with no pronounced indication of any superiority of the experimental group over the control. If individual charts are examined it is found that the status of 22 experimental subjects was improved, that of 11 was the same and that of 17 was actually lower than at the beginning, in the control group the status of 15 was improved, that of 7 was the same and that of 28 was worse than at the beginning. When the final status of the partners is compared, moreover, in 30 pairs, or 60 per cent, it is seen that the

experimental child had a somewhat higher reading than the control partner with whom he was matched at the beginning, in only 12 pairs, or 24 per cent, did the control child have the advantage. These evaluations, however, exaggerate the differences between the groups. From

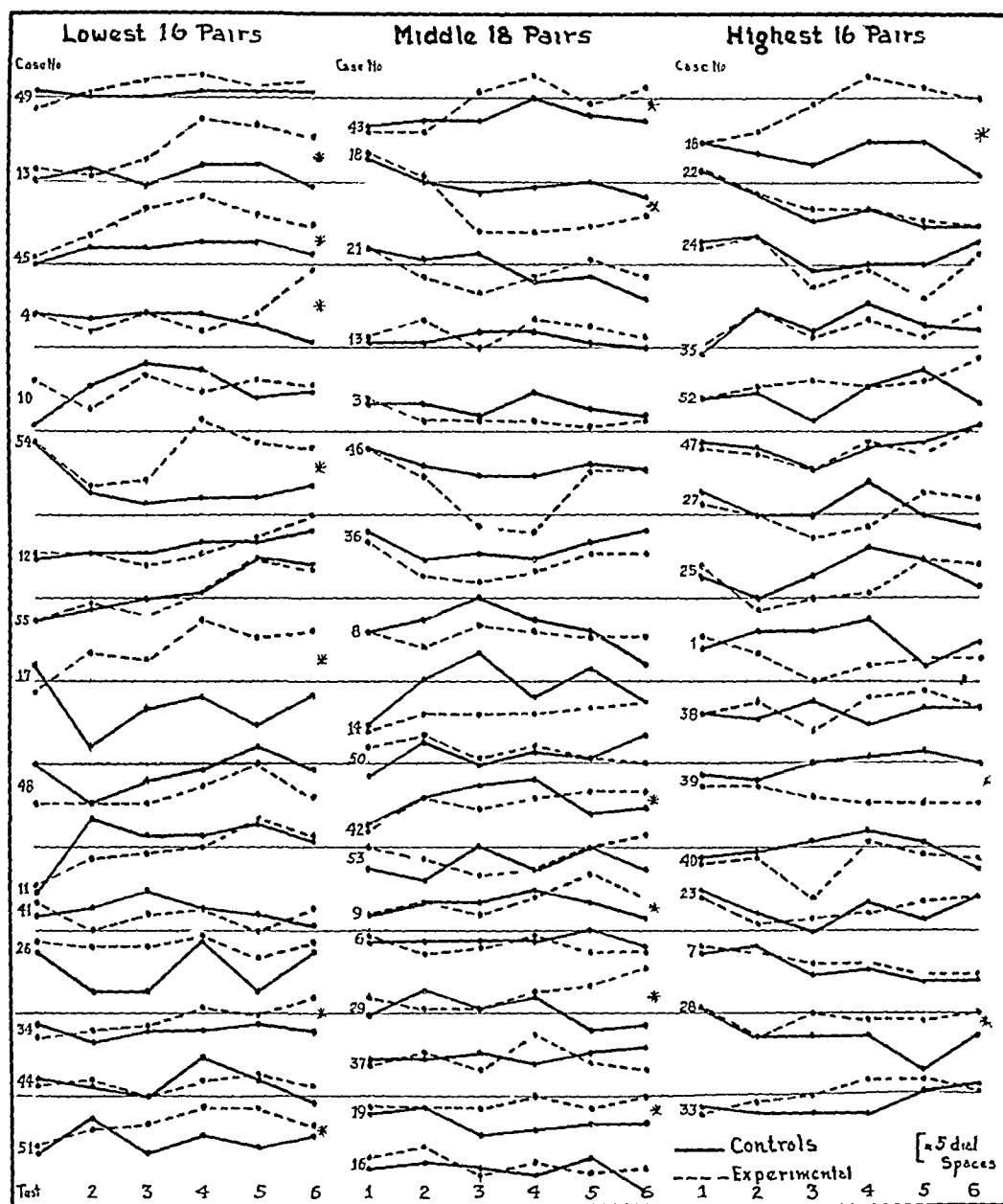


Chart 2—Readings for each of the 50 pairs of children in each test

actual inspection of the chart, only the ones marked with an asterisk seem to us to be real differences. There were only 16 such pairs, and in 14 of these the advantage was with the child to whom the supplement was given.

It is of special interest to note again that it was in the lowest group that the improvement was most marked. Of the 14 children showing

decidedly better progress than their controls, 7 were in this low group, 5 were in the middle group and 2 were in the highest group. This is in accord with the claims of Booher and others that the test is most useful for measuring progress in cases of marked dysadaptation. It should be pointed out, however, that 46 of the 50 experimental subjects were in the borderline or the subnormal zone at the beginning and should presumably have responded to the supplement if the test were a precise measure of vitamin A stores.

To sum up the results of this portion of the study, there appears to be little doubt that the supplement did cause some improvement. The experimental group showed a greater advance in mean dial reading, a somewhat greater increase in the percentage of children in the normal zone and more children whose gains exceeded those of their partners. The results were not sufficiently clearcut, however, to warrant the conclusion that a child's stores of vitamin A bear a direct relation to the biophotometer readings. This is shown by the facts that more than half the children receiving the supplement failed to improve and that 26 per cent of the control children gained more than their partners. It would seem, then, that while the test may be of some value in showing the relative progress of groups, its usefulness in determining the nutritional status for vitamin A of individual subjects is doubtful. Since, however, most of the improvement noted was made by the children for whom the test values were lowest, it may be concluded that a child with a test value in the very low zone is more apt to show sub-clinical vitamin A deficiency than one for whom a higher test value is recorded.

EFFECT OF A DEPLETION DIET ON BIOPHOTOMETER READINGS

The most crucial attack on the problem of the validity of the test was to study the effect of a diet low in vitamin A on the biophotometer readings to ascertain whether the results reported by Jeghers and by Booher for 1 subject each could be reproduced. Six women served as subjects. These subjects ate a constant weighed diet which as calculated contained less than 100 units of vitamin A per day. All subjects ate identical amounts by weight of any food which contained a significant amount of vitamin A or carotene, but certain foods, such as cakes made from hydrogenated fat, sugar, egg white and white flour, were allowed ad libitum. The plan was to continue the diet until the subjects were definitely night blind, as judged by the test, and then to determine the amount of a vitamin A supplement required to restore them to normal. Unfortunately this was not possible except in 2 cases, as the school year closed before this end was accomplished. Three subjects were on the depletion diet for twenty-five, thirty and forty-four days respectively,

and the remaining 3 were on this diet for one hundred and twenty-three days, having each received a small supplement, of 1,000 units, of vitamin A on the sixty-fifth day and again on the seventy-second and seventy-sixth day

The individual biophotometer readings for the six subjects during these periods are shown in chart 3. It will be noted that only 2 of the

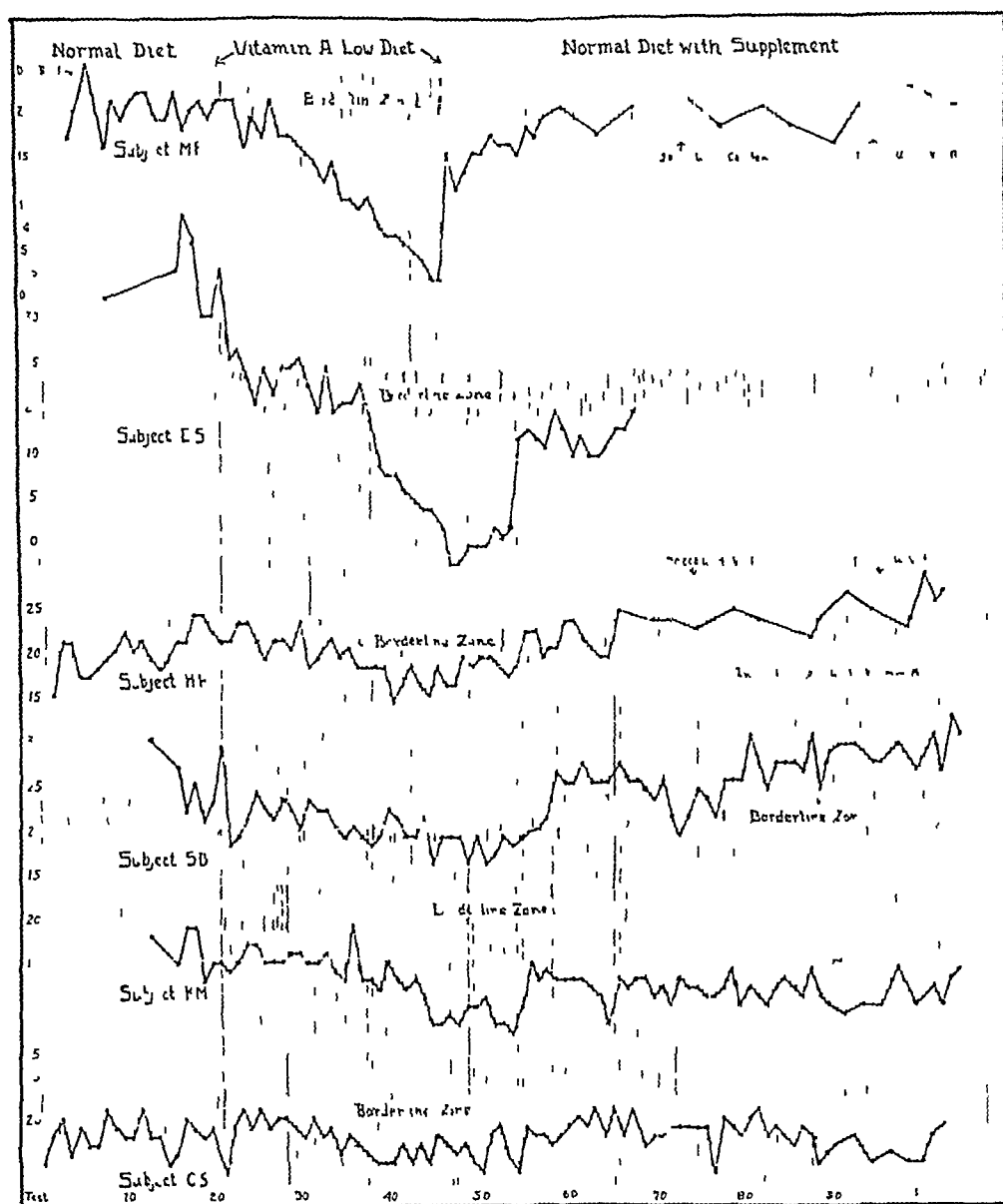


Chart 3—Individual readings for the 6 subjects on the depletion diet

6 subjects showed the expected drop in biophotometer reading. Both of these showed a significant change at the end of two weeks and dropped rapidly thereafter. M F at twenty-five days exhibited definitely impaired dark adaptation, in fact, the readings were as low as the instrument used would measure. She was then given 100,000 units

of vitamin A in the morning and tested at two hour intervals during the first day. Her response was prompt and spectacular, the readings were almost up to their original level by the end of the day. In the case of E. S. also the values dropped rapidly on the depletion diet from the original level of 35 to 5 at the end of forty-five days, they likewise rose immediately when she was given 2,000 units of vitamin A. Had only these 2 subjects been studied, conclusions as to the validity of the test would have seemed warranted. The other 4 subjects, however, did not exhibit this response, though 3 of them continued the experiment for four months. Their day to day readings showed much variation, with occasionally a small drop and then a rise suggestive of improvement. Unfortunately, however, these rises were not coincident with the periods of supplementation. In fact, one could not by inspection of the graphs of these 4 subjects determine which were periods of depletion and which periods when supplements were being employed.

The most obvious explanation for the variation in response of these 6 subjects is that there must have been a difference in their stores of vitamin A. A study of their dietary histories does not support this belief. Of the 2 subjects who showed decreased readings, 1 had a history of a low intake of vitamin A, but the second apparently had an exceptionally high intake. Of the 4 subjects who showed no significant change in readings during the period of depletion, 3 had dietary histories showing a very high intake of vitamin A, while the fourth had only a fair dietary history. Moreover, if the biophotometer test is a valid indication of the body's stores of vitamin A, the subjects for whom the lowest original readings were recorded should have been the ones to respond by decreased readings when placed on a diet deficient in vitamin A, but this was not the case. Two subjects whose original readings placed them in the borderline or the deficient zone (G. S. and K. M.) showed no significant drop after four months, and 1 subject (E. S.) whose readings went down rapidly with the depletion diet had the highest original readings of any in the group.

The most interesting case in the entire study was that of G. S., who had been given frequent tests with the biophotometer for nine months previous to the time she was placed on the deficient diet, so that a consecutive study of the readings for over a year was possible. When she was first tested, the readings classified her at the upper limit of the subnormal zone. Since an ophthalmologic examination revealed no cause for these low readings, an attempt was made to increase them by supplements of vitamin A. The dose varied from 20,000 to 100,000 units of vitamin A per day. Various supplements were used in turn, halibut liver oil, cod liver oil concentrate, cod liver oil and carotene. This subject was given a total of 157 biophotometer tests during one year. The first reading in the recovery period for all of her tests are

shown in chart 4. It will be noted that regardless of whether this subject received 100,000 units of vitamin A per day or less than 100 units there was no tendency for the general trend of the readings to vary. The mean for the 157 tests was 17.6 with a standard deviation of 1.7 for the first reading in the recovery period and 56.9 with a standard deviation of 4.6 for the last.

It is possible, of course, to explain the failure of this subject to respond to changes in her intake of vitamin A if it is assumed that the standards were too high and the capacity for storage of vitamin A of the same order as that found in experimental animals. If her adaptation was normal at the outset, increasing the vitamin A intake even up to 100,000 units would, of course, not effect any change. Furthermore, if a considerable proportion of the large excess of vitamin A ingested during the supplementation period was stored, it might easily

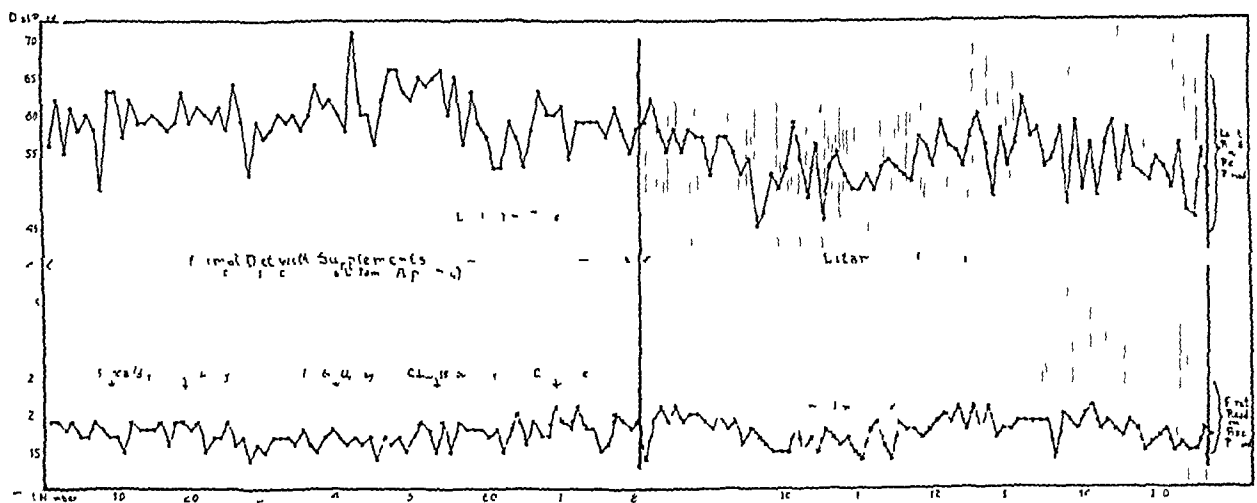


Chart 4—First and last readings in the recovery period for the one hundred and fifty-seven tests given subject G. S. The intake of vitamin A varied from 100,000 to 100 units per day.

have been sufficient to supply her during the four months of depletion. This would seem a plausible explanation. It is difficult, however, to reconcile it with the report of Jegheis on a subject who after large supplements of vitamin A showed lowered biophotometer readings within a week on a deficient diet.

The results in these 6 cases emphasize the dangers of drawing conclusions from findings on 1 or 2 subjects. The fact that 2 subjects showed decidedly lowered readings after twenty-five and forty-four days respectively on a deficient diet must be interpreted to mean that the results of the biophotometer test are influenced by the vitamin A intake of some persons. On the other hand, the facts that 4 subjects failed to respond after four months on the depletion diet and that the response of the 6 subjects was not consistent with either their original

biophotometer readings or their dietary histories indicate that the relation between the test and the vitamin A stores is certainly not clearcut and infallible

COMMENT

The evidence presented shows clearly that there is some relation between biophotometer readings and vitamin A stores. Three lines of evidence support this contention. 1 The mean readings of children in the higher socioeconomic group were significantly higher than those in the lower socioeconomic group. 2 The children who were given a supplement showed a slight improvement over their matched controls. 3 Two subjects on a diet low in vitamin A responded with lowered readings and immediately improved when a supplement was given.

While this evidence is in support of the validity of the test, it does not warrant the contention that the test can be used as a diagnostic measure for determining deficiency in vitamin A, nor does it signify that changes in readings are necessarily associated with changes in vitamin A stores. The following evidence makes such conclusions unwarranted. 1 Many subjects known to be living on a diet rich in vitamin A were classified by the readings as subnormal. 2 The majority of the children who were given a supplement never attained "normal" readings. 3 The relation of vitamin A to biophotometer readings was not consistent, in that 30 per cent of the children in the control group who gave original low readings improved without any supplement while 56 per cent of the experimental group who received one did not. 4 Four out of 6 subjects did not respond to a diet low in vitamin A with lowered readings. 5 There was considerable variation in readings for the same subject on successive tests. Thus many subjects tested under standard conditions were classified as normal on one test and borderline or even subnormal on the next.

Part of this negative evidence is removed if one admits that the suggested standards are too high. Such an admission carries with it the necessity of recognizing that the incidence of mild vitamin A deficiency is much lower than has been reported. Moreover, even with lower standards for normal readings there would be some subjects giving low readings who had normal stores and some giving higher readings who had poor stores. The question of the value of the biophotometer test, then, is dependent on the purpose for which the test is used and the interpretation given to the results. It has been shown that the means of the biophotometer readings for large groups of subjects remain fairly constant from test to test and consequently could be used to place the groups in relation to each other. In well controlled studies the test could also be used to measure the effect of a supplement by noting the effect on the mean for the group. When, however, the individual subject is considered, the test is much less useful.

It does not serve satisfactorily for diagnosing mild vitamin A deficiency. It is true that a subject who gives very low readings is more apt to be deficient than one who gives high readings, but a change in any one subject's readings from test to test is as apt to be due to chance as it is to be related to his nutritional status for vitamin A. The procedure recommended is that of testing persons frequently and judging the effect of a supplement by comparing their progress with that of well matched controls. This method is, however, expensive of time and is warranted only when there is no better means available for measuring vitamin A deficiency. The situation is similar to the use of capillary fragility in measuring vitamin C deficiency. In a well controlled study, until better methods are available, both tests might be advantageously used, together with other measures of nutritional status, to follow the progress of a group, but the interpretation of results for individual subjects should be made with caution.

It should be emphasized that these conclusions are concerned not with the fundamental problem of whether tests of dark adaptation can be used to determine vitamin A stores but merely with the usefulness of the biophotometer for this purpose. It is recognized that some of the difficulties encountered are mechanical ones which presumably could be remedied in the construction of the instrument used. All tests which depend on the subject's stating when he sees a point of light, however, carry a subjective element, and errors of interpretation are apt to occur unless the reliability of the test is determined and the study carefully controlled.

Certainly the theory behind the test is sound, and the results even with an instrument as simple in construction as the biophotometer, are sufficiently encouraging to warrant further study both for improving the instrument for measuring dark adaptation and for determining its validity as a measure of nutritional status for vitamin A. Whatever may be the outcome, great credit is due to Jeans and his co-workers and to the makers of the biophotometer for taking the initial step in this new line of nutritional research.

SUMMARY

The results of over 2,000 biophotometer tests on 459 persons were analyzed to determine the reliability of the test and its validity as a measure of the nutritional status for vitamin A. The outstanding findings follow:

1. Single tests of a subject are unreliable, as the readings may vary so widely on successive tests, even with a constant dietary regimen, as to change his classification to or from the normal or the subnormal zone. The general trend, however, of the readings for the same subject is fairly constant, and the test, therefore, can be used to determine the

level for a person or for a group if a sufficient number of readings are obtained to determine their variability. This procedure is time consuming and practically rules out the test, even if it were valid, for routine clinical use.

2 For children from a high socioeconomic level the biophotometer readings were significantly higher than for children from a low socioeconomic level. Only 26 per cent of the children in the superior group, however, gave readings which classified them as "normal" according to the Jeans standards.

3 A supplement given to 50 children for whom the original readings were low caused no significant difference in the mean readings of the group as a whole as compared with those of a matched group of 50 controls. More than half of the children receiving the supplement, moreover, failed to improve, and 26 per cent of the control children gained more than did their partners. It is worthy of note, however, that in 14 of the 16 pairs in which a real difference was evident the odds were in favor of the child who received the supplement.

4 A depletion diet caused a significant change in the biophotometer readings for only 2 of 6 subjects, although 3 of the others remained on the diet for four months. The response of the 6 subjects to the depletion diet was not consistent with either their original biophotometer readings or their dietary histories.

These results make it evident that, although some relation exists between the biophotometer readings and vitamin A nutrition, the relation is not close enough to warrant the use of the test as a means of diagnosing subclinical vitamin A deficiency. The basis idea, however, of the use of measurements of dark adaptation for determining deficiencies of vitamin A seems promising and worthy of further experimentation.

Hazel Lapp, Berniece Anderson and Helen Parks gave technical assistance in this study, performing many of the tests. Helen Heinzelman collaborated in the section on the effect of a depletion diet on biophotometer readings. Miss Heinzelman carried out the work on 2 subjects and has reported the details in her Master's thesis, "The Relation of Vitamin A Intake to Visual Adaptation to Light and Dark as Determined by the Biophotometer," University of Chicago, 1939.

INFANTILISM IN ULCERATIVE COLITIS

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Infantilism has been frequently seen as a sequela of such chronic debilitating diseases as chronic renal disease,¹ congenital and rheumatic heart disease, diabetes mellitus, avitaminosis, congenital syphilis, Addison's disease,² Still's disease³ and congenital hemolytic icterus.⁴ Infantilism has been frequently reported in gastrointestinal disorders, especially in celiac disease and idiopathic steatorrhea.⁵ In one series of 15 cases of idiopathic steatorrhea, characteristic stigmas of infantilism appeared in 10.^{5a} It has been found also in cases of chronic intestinal tuberculosis.² I have seen 1 such case in the past year.

Despite the frequent mention of infantilism associated with the gastrointestinal disorders mentioned, it has not been reported in ulcerative colitis. Bargaen,⁶ in summarizing the sequelae in 1,500 cases of ulcerative colitis, did not mention infantilism, nor did he, Jackman and Kerr,⁷ speak of it in discussing another series of 871 cases, in 243 of which the patients were in the second and third decades of life. Mackie,⁸ in his report on the deficiency states in 75 cases of ulcerative colitis, did not mention infantilism, nor did Lups⁹ or Rankin, Bargaen

From the Medical Service of Dr. L. Lichtwitz, Montefiore Hospital

1 Ellis, A., and Evans, H. Renal Dwarfism, *Quart J Med* **2** 231, 1933

2 Apert, E. Infantilism, translated by R. W. B. Ellis, London, M. Hopkinson, 1933

3 Rosenfeld, A. S. Still's Disease, *J A M A* **69** 115 (July 14) 1917

4 Langston, W. Infantilism in Congenital Hemolytic Jaundice, *South M J* **28** 316, 1935

5 (a) Bennett, T. I., Hunter, D., and Vaughn, J. M. Idiopathic Steatorrhea, *Quart J Med* **1** 603, 1932 (b) Thaysen, T. E. H. Idiopathic Steatorrhea, *ibid* **4** 359, 1935 (c) Hanes, F. M., and McBryde, A. Identity of Sprue, Nontropical Sprue and Celiac Disease, *Arch Int Med* **58** 1 (July) 1936

6 Bargaen, J. A. Management of Colitis, New York, National Medical Book Company, Inc., 1936

7 Bargaen, J. A., Jackman, R. J., and Kerr, J. G. Life Histories of Patients with Ulcerative Colitis, *Ann Int Med* **12** 339, 1938

8 Mackie, T. T. Ulcerative Colitis Factor of Deficiency States, *J A M A* **104** 175 (Jan 19) 1935

9 Lups, S. Vaccine Therapy in Ulcerative Colitis, *Am J Digest Dis & Nutrition* **2** 65, 1935

and Buie¹⁰ in their detailed discussion of the disease. It probably has been seen but not reported.

In the past two years at Montefiore Hospital infantilism has been observed in 3 cases of ulcerative colitis.

REPORT OF CASES¹¹

CASE 1—L. E., a 17 year old white youth, was admitted to the private pavilion on Aug. 17, 1937. His history was uneventful until 1932, when, at the age of 12 years, he was operated on for a rectal abscess and fistula. He lost considerable weight and during his slow convalescence began to have diarrhea, which continued intermittently until 1936. At this time failure of physical development was noted, and he was given anterior pituitary extract parenterally. There was some improvement of the gastrointestinal symptoms and a gain in weight. Soon after he began to have severe cramps and fever in addition to the diarrhea and on admission was having eight bowel movements a day.

Physical Examination—The patient was afebrile, emaciated and poorly developed, appearing about 12 years of age rather than his stated age of 17. The heart, lungs and abdomen appeared normal on physical examination. The blood pressure was 90 systolic and 50 diastolic. There was no pubic, axillary or facial hair. The penis was infantile, the right testis, small but descended. The left testis was not palpable in the scrotum or inguinal canal. He weighed 50 pounds (22.7 Kg.).

Laboratory Data—The hemoglobin content was about 4.5 Gm. except for temporary remissions after blood transfusions. The stools were liquid and brown and contained gross blood and mucus. Studies of fat in dry stools showed 72 per cent total fat, with 35 per cent fatty acids and 37 per cent neutral fat.

Course—He was treated with a high vitamin diet, vitamin C, gonadotropic substance from the urine of pregnant women, liver extract given intramuscularly and a series of transfusions. Little improvement resulted. Bilateral parotitis, gangrenous stomatitis and bronchopneumonia developed, and he died on Sept. 10, 1937.

*Postmortem Examination*¹²—Bilateral bronchopneumonia, bilateral parotitis, gangrenous stomatitis, gingivitis and esophagitis were observed. There were old infarcts of the spleen and evidences of old rheumatic infection of the mitral valve. The gastrointestinal tract revealed an edematous intestinal mucosa, with extensive confluent ulceration of the entire ileum and colon. The glomerular and reticular layers of the adrenal cortex were intact, but there were degenerative changes in the fascicular layers. There was marked hypoplasia of the tubules of the testes, with virtually no cellular differentiation. Spermatogenesis was absent. The interstitial cells had large vesicular nuclei with clear cytoplasm.

10 Rankin, F. W., Bargen, J. A., and Buie, L. A. *The Colon, Rectum and Anus*, Philadelphia, W. B. Saunders Company, 1932.

11 Case 1 was a private case of Dr. L. Lichtwitz, cases 2 and 3 were from the gastrointestinal division of Dr. J. L. Kantor.

12 Postmortem examination in case 1 was done by Dr. William Sternberg, in case 2, by Dr. David Silberman. The special studies of the pituitary were made by Dr. Charles Spark.

CASE 2—R. H., a white boy 15 years of age, was admitted to the medical service in 1936 because of bloody diarrhea. In infancy he had had eczema, at the age of 9 years, typhoid fever. Between the ages of 10 and 12 years he had developed normally but was always small of stature. In 1934, at the age of 13, he began to have attacks of bloody diarrhea and abdominal cramps. He was hospitalized with some improvement but had an exacerbation with recurrence of abdominal complaints in 1936, when he was again hospitalized. At that time, at the age of 15, he was noted to be physically immature, and the diagnosis of secondary infantilism was made. He was treated with antidyenteric serum without results and then transferred to Montefiore Hospital.

Physical Examination—The patient was undernourished and underdeveloped and seemed much younger than his stated age of 15. He weighed 63 pounds (28.6 Kg.) and was 59 inches tall (149.9 cm.). There was no hair on the face, axillae or pubis. The heart was normal, the lungs were clear. Neither liver nor spleen was palpable, nor were there other abdominal masses.

Laboratory Data—Analyses of the urine showed some albumin and an occasional cast. The hemoglobin content was 80 per cent on admission but soon dropped to 60 per cent, at which it remained. The urea nitrogen content of the blood was 7.1 mg. per hundred cubic centimeters and the dextrose content 84 mg. The serum proteins were 5.8 Gm. per hundred cubic centimeters with 3.2 Gm. of albumin and 2.6 Gm. of globulin. The stools constantly contained gross or occult blood. Roentgen studies of the gastrointestinal tract were interpreted as typical of colitis gravis of the entire colon.

Course—After one year's supportive therapy, the patient was discharged unimproved in May 1937. He did well for a while, but his general condition became worse, although he had but three or four bowel movements daily. He was readmitted in June 1938.

Readmission—On admission he weighed but 51 pounds (23.1 Kg.), 12 pounds (5.4 Kg.) less than he had weighed on the previous admission two years before. His height was the same, he was pale and emaciated, and his apparent age was 12 years. His voice was high pitched. There was no hair on the face, pubis or axillae. The heart and lungs appeared normal on physical examination. The liver was enlarged down to the umbilicus, and the spleen was palpable. The skin was dry and hardened. The penis was small and atrophic. The testes were small and soft.

Laboratory Data—The hemoglobin content was 36 per cent, with 2,600,000 erythrocytes. The serum proteins were 6.5 Gm. per hundred cubic centimeters, with 2.1 Gm. of albumin and 4.4 Gm. of globulin. The urea nitrogen content of the blood was 6.2 mg. per hundred cubic centimeters, the calcium content 8.7 mg. and the phosphorus content 3.7 mg. The dextrose tolerance test with 30 Gm. of dextrose showed a fasting blood sugar content of 90, with a peak of 120 in one hour. There was no blood in the stool. Roentgen and fluoroscopic studies revealed pronounced enlargement of the transverse and descending aorta compared with the films made on previous admission. Roentgenograms of the skull and long bones demonstrated some osteoporotic changes. The congo red test showed 100 per cent retention of the dye in the tissues after one hour, indicating amyloidosis.

Course—The patient was fed a high protein diet and given vitamin preparations, iron and liver by mouth. Nevertheless, he declined steadily and on Oct. 21, 1938, died, after three days of continuous blood diarrhea.

Postmortem Examination—The heart weighed 100 Gm. There were no gross or microscopic abnormalities. The supravalvular portion of the aorta showed a

saccular dilatation, with a ring of narrowing. The descending portion of the thoracic aorta showed fusiform dilatation and at the level of the diaphragm appeared to be narrowed by a definite band of intima. Microscopically there was extensive destruction of the inner and outer elastic membranes and muscle fibers of the media of the aorta. The endothelial lining was fairly well preserved. In the outer layer of the adventitia were numerous large collections of chronic inflammatory cells with areas of hyalinization. The intimal coat had a similar appearance.

The gastrointestinal tract revealed a normal esophagus. The jejunal mucosa was slightly injected. The ileum displayed several patches with atrophic gray mucosa. The distal 12 inches (30.5 cm) of the ileum and the entire colon showed a pink-tinged mucosa with pinpoint hemorrhages. There were several areas, especially in the sigmoid, where the mucosa was atrophic and gray. Otherwise the mucosa appeared hypertrophic and in numerous areas formed what appeared to be sessile papillae. Microscopically the mucosa and submucosa of the distal half of the ileum and the entire colon were extensively infiltrated with lymphocytes, plasma cells and a few eosinophils. The muscular coat was thickened and invaded by lymphocytes and plasma cells. The outer muscular coat showed nuclear shrinkage surrounded by a clear zone and honeycombed appearance. There were patches of amyloid beneath the epithelium in the small and large intestine.

The liver and spleen were both enlarged and contained considerable amyloid deposits. There was also amyloidosis of the kidney, with many glomeruli partly or completely replaced by amyloid. The pancreas was grossly normal but microscopically showed deposition of amyloid.

The parathyroids were enlarged, with moderate and marked replacement of the cells with amyloid. The thyroid was small, the follicles, large and filled with layered pink colloid. The adrenals were normal in size and showed fatty infiltration in all zones. There was marked amyloid replacement of the fascicular zone. Only a few pigmented cells remained. There was fibrosis of the medulla.

The testes were small and microscopically prepubertal. The tubules were small. There were no mitotic figures or any evidence of maturation. The interstitial cells were swollen, with round vesicular nuclei and colorless cytoplasm.

Because the literature contains no previous extensive pituitary studies in cases of secondary infantilism, the studies of the gland in this case are reported in detail.

The gland weighed 360 mg. It was sectioned in five sagittal levels. The sections were stained in Mallory's triple stain preceded by hematoxylin.

The most striking change in the anterior lobe was that seen in the nuclear elements of all the cells. All the nuclei were large and vesicular and many possessed large nucleoli. There was a definite increase in the number of basophil cells and a decrease in the number of acidophils. The basophil cells were large and had abundant deep-staining granules and showed little vacuolization. There were many small nodules of adenomatoid hyperplasia of the basophilic elements. There were scattered small foci of transitional basophils that were growing in the form of a syncytium. There were no colloid basophils.

The acidophil cells were most numerous in the region of the pars intermedia, and there their arrangement was rather atypical. The cells showed marked variation in size and shape and in places seemed to be growing in irregular anastomosing strands instead of the usual growth in cell columns and follicles. Many pyknotic nuclei were present in these atypical areas.

There were many "large chromophobe cells" These had large vesicular nuclei and abundant watery cytoplasm containing scattered grayish granules which did not take either the acid or the basic stain Many of these cells were arranged in follicles with retention of colloid droplets in the center, and both types of chromophil cells were intermingled among them

A striking feature of the anterior lobe was the presence of large numbers of follicles containing colloid, and in some instances the colloid appeared to be calcified A small proportion of the basophil cells were extremely bizarre, some reaching a giant size with abundant granules Many binucleated cells were present

The capillary bed of the anterior lobe appeared to be compressed by the hyperplastic growth of the cellular elements There were few typical chromophobe cells In many areas the nuclei of all the cell types were so closely aggregated that the growth appeared to resemble a syncytium The residual lumen was present, and it was filled with colloid

There was only an occasional basophil cell infiltrating the posterior lobe Few pigmented pituicytes were present in the posterior lobe

CASE 3—H F, a white youth aged 17, was admitted to the medical service in January 1938, because of bloody diarrhea Until the age of 11 he had been a normal boy, with normal development and stature In 1931 there was a sudden onset of fever, with pains in the joints and purpura These symptoms lasted several months, at the end of which bloody diarrhea developed, for which he was hospitalized There were exacerbations and remissions In 1935, after a particularly severe bout, he was again hospitalized, and roentgen studies suggested the diagnosis of ulcerative colitis After therapy with vaccines was ineffectual, ileostomy was done in 1936, followed by resection of half of the colon There was no marked improvement, however, and he entered Montefiore Hospital complaining of weakness, anorexia and diarrhea, with six to ten black stools daily

Physical Examination—The patient was markedly emaciated, undernourished and underdeveloped, seeming not more than 12 years of age, despite the stated age of 17 He spoke in a childish, high-pitched voice The face, axillas and pubis were devoid of hair There was marked gingivitis and pyorrhea The teeth were poor and carious, and the gums were red and bled readily There was an ileostomy in the midline The penis was small, as were the testes, which were palpable at the external inguinal rings The fingers and toes were clubbed

Laboratory Data—There was a flattening of the dextrose tolerance curve, with a fasting sugar content of 70 mg per hundred cubic centimeters and a peak of 103 in one hour Gastric analysis showed free acid only after administration of histamine The urea content of the blood was but 4.9 mg per hundred cubic centimeters The hemoglobin content was 56 per cent, with 3,600,000 erythrocytes Roentgen studies of the gastrointestinal tract revealed the ileosigmoidostomy with resection of the colon down to the iliac portion Proctoscopic examination revealed hemorrhagic proctitis

Course—Therapy consisting of diet, iron, vitamin C and liver was attempted The hemoglobin content increased to 65 per cent, the weight to 74 pounds, and the patient was discharged in September 1938, somewhat improved, with the diagnosis of ulcerative colitis

COMMENT

Infantilism in chronic disease is characterized by retardation or absence of sexual development, usually accompanied by diminished

growth Although usually considered secondary to the underlying debilitating condition, both disorders in some cases have been considered to be due to a primary disease of the pituitary-hypothalamic complex Chown and Lee,¹³ in a careful study of a case of renal dwarfism, stated that both the renal disease and the endocrinopathy were due to a lesion in the pituitary-hypothalamic complex, with encephalitis as the probable etiologic agent Gibson and Fowler,¹⁴ reporting 8 cases of infantilism associated with diabetes mellitus, noted that the onset of the disease occurred in all cases after the cessation of development and suggested that the diabetes was not the cause of the infantilism but that both were due to a central lesion

For the most part, however, infantilism in chronic disease is considered secondary and has been demonstrated, in some few cases, to be reversible Apert² reported the case of a 17 year old diabetic patient who, treated before the insulin era, displayed marked physical and sexual immaturity Insulin became available, and within one year of its use normal physical and sexual maturity was attained Langston¹ cited the case of a 17 year old boy with congenital hemolytic icterus, whose development was that of an 11 year old child After removal of the spleen and the use of anterior pituitary extract, he rapidly reached normal physical development

Secondary infantilism in the chronic diarrheas is almost entirely due to the effects of the diarrhea, depriving the growing organism of an adequate supply of the substances needed for normal maintenance, maturation and growth The faulty absorption from the gastrointestinal tract in such diseases creates not only a caloric deficiency but also deficiencies of nitrogen, vitamins and minerals The need of the growing organism for these substances is greater during the period of maturation and, as was pointed out by Sherman,¹⁵ is so urgent that a shortage of any essential factor becomes more quickly and strikingly apparent and is likely to be more harmful than in the case of the maintenance metabolism of the adult It is not surprising, then, that infantilism occurs most strikingly in patients who are ill during the period of physical and sexual maturation This was true in my cases and in the cases of steatorrhea described by Thaysen,¹⁶ by Hanes and McBryde^{5c} and by Bennett, Hunter and Vaughn^{5a}

13 Chown, B, and Lee, M Renal Rickets and Dwarfism as a Pituitary Disease, *Am J Dis Child* **53** 117 (Jan, pt 1) 1937

14 Gibson, R B, and Fowler, W M Infantilism and Diabetes Mellitus Report of Eight Cases, *Arch Int Med* **57** 695 (April) 1936

15 Sherman, H C Chemistry of Food and Nutrition, New York, The Macmillan Company, 1938

16 Thaysen, T E H Idiopathic Steatorrhea London Oxford University Press, 1931

Of all deficiencies, the most important is probably that of available calories. The interference with adequate absorption from the gastrointestinal tract by chronic diarrhea deprives the growing organism of an adequate supply of energy. Such caloric insufficiency in other states of malnutrition has been found both clinically¹⁷ and experimentally¹⁸ to have marked effects on maturation and growth. Stefko¹⁷ in his studies on malnutrition found cryptorchism frequent in adolescent boys. Puberty was greatly retarded, and the external genitalia in general remained poorly developed. Microscopically the testes were prepubertal in appearance. The pituitaries of such boys seemed unaffected except for slight basophil hyperplasia.

In addition to caloric inadequacy deficiencies of nitrogen, vitamins and minerals play an important role in producing infantilism in the chronic diarrheas. In ulcerative colitis Welch and his co-workers¹⁹ have demonstrated a negative nitrogen balance, which is increased during the more active stages of the disease. The need of the growing organism for nitrogen is great, and an inadequate supply, especially of the essential amino acids, can raise havoc with processes of growth.²⁰

Specific vitamin deficiencies are frequently present in both ulcerative colitis²¹ and steatorrhea.²² Their effect experimentally, especially on the endocrine glands, is profound, and clinically they must play an important role in the disturbance of growth and endocrine balance seen in chronic diarrheas.

Experimentally, lack of vitamin A, riboflavin and vitamins D and E all have been shown to have a profound influence on the growth of animals.²³ Deficiency of vitamins A, B₁ and E have specific effects on the endocrine glands. Deficiency of vitamins A and E causes testicular

17 Stefko, W, cited by Jackson, C M. Recent Work on the Effects of Inanition and Malnutrition on Growth and Structure, *Arch Path* **7** 1042 (June) 1929.

18 Waters, H S. Capacity of Animals to Grow Under Adverse Conditions, *Agric Sc* **29**:71, 1908, cited by Sherman¹⁵.

19 Welch, C S, Wakefield, E, and Adams, M. Metabolic Studies in Ulcerative Colitis, *J Clin Investigation* **16** 167, 1937.

20 Smith, A H. Phenomena of Retarded Growth, *J Nutrition* **4** 427, 1931.

21 Barnes, J M. Typical Pellagra Syndrome Developing in Patient with Ulcerative Colitis, *Ann Clin Med* **4** 552, 1926. Mackie⁸.

22 Thaysen, T E H. Zwei Falle von idiopathischer Steatorrhoe, mit besonderer Berücksichtigung der Diagnose und des Vorkommens von Symptomen einer Endokrinopathie und Avitaminose, *Arch f Verdauungskr* **61** 225, 1937, footnote 16.

23 (a) McCollum, E V, and Simmonds, N. Newer Knowledge of Nutrition, New York, The Macmillan Company, 1929. (b) Hogan, A G. Riboflavin Physiology and Pathology, *J A M A* **110** 1188 (April 9) 1938. (c) Martin, G J. Vitamin E, *J Nutrition* **13** 679, 1937.

atrophy and inhibition of spermatogenesis²⁴ Microscopically the pituitaries of animals so affected show basophilic hyperplasia and have increased gonadotropic effect²⁵ This response is similar to, but not as extensive as, that to castration²⁶ It is noteworthy that the pituitary in case 2 had a similar microscopic picture In deficiency of vitamin B₁, diminution in secretion of androgen has been demonstrated^{26a}

The constant loss of calcium often resulting in negative calcium balance in these diseases²⁷ is important not only in the generalized osteoporosis seen so frequently²⁸ but in the production of gonadal degeneration and arrest of growth Simmonds²⁹ found that the rate of growth of young rats was halved by lowering the calcium intake Yamasaki³⁰ found that salt deficiencies as well as vitamin deficiencies resulted in disturbance of spermatogenesis in the testis and follicular atrophy in the ovary Hirabayshi³¹ reported that of all the mineral deficiencies, lack of calcium, magnesium and phosphorus had the most striking effects

The effects of vitamin deficiencies may tend to enhance and continue the pathologic processes causing them The production of ulcerative colitis in monkeys by deficiency of vitamin A has been described,³² and it may be that chronic deficiency of vitamin A in long-standing

24 (a) Sutton, T S, and Brief, B J Cellular Changes in the Hypophyses of Vitamin A Deficient Rats, *Endocrinology* **23** 211, 1938 (b) Wolbach, S B, and Howe, P R Tissue Changes Following Deprivation of Fat Soluble A, *J Exper Med* **42** 753, 1925 (c) Mattill, H A Vitamin E, *J A M A* **110** 1831 (May 28) 1938 (d) Nelson, W O Studies on the Anterior Hypophysis Anterior Hypophysis in Vitamine E-Deficient Rats, *Anat Rec* **56** 241, 1933

25 Mason, K E, and Wolf, J M Physiological Activity of the Hypophysis of the Rat Under Various Experimental Conditions, *Anat Rec* **45** 232, 1930 Footnote 26

26 Sutton and Brief^{24a} Nelson^{24d}

26a Moore, C R, and Samuels, L T Action of the Testes Hormone in Correcting Changes Induced in Rat Prostate and Seminal Vesicles by Vitamin B Deficiency or Part Inanition, *Am J Physiol* **96** 231, 1931

27 Thaysen¹⁶ Welch, Wakefield and Adams¹⁹

28 Bennett, Hunter and Vaughn^{5a} Thaysen, footnotes 5 b and 16 Case 2 of this report

29 Simmonds, N Observations on the Rearing of the Young, *Am J Hyg* **4** 1, 1924

30 Yamasaki, Y Experimentelle Untersuchungen uber den Einfluss des Vitamins oder Zellsalz mangels auf die Entwicklung von Spermatozoen und Eiern, *Virchows Arch f path Anat* **245** 513, 1923

31 Hirabayshi, N Experimentelle Untersuchungen uber den Einfluss der Salze auf die Entwicklung der Spermatozoen bei weissen Mause, *Virchows Arch f path Anat* **250** 661, 1924

32 Bellows, J Biochemistry of the Lens Influence of Vitamin C and Sulfhydryls on the Production of the Galactose Cataract, *Arch Ophth* **16** 762 (Nov) 1936

gastrointestinal disease may extend the primary pathologic lesions.³³ The adrenal degenerative changes consequent to malnutrition and vitamin deficiency may interfere with the absorption of fat in the utilization of riboflavin.^{33a}

The exact role played by these deficiencies in the slowing or halting of cellular metabolism is unknown for the most part, but something is known of the place of the vitamins in the cellular scheme of things. Vitamin B₁ is intimately concerned with the normal metabolism of carbohydrates, more particularly with one of the intermediate products, pyruvic acid. It acts as carrier of oxygen and seemingly is necessary for the completion of normal carbohydrate oxidation.³⁴ Riboflavin is an essential part of the yellow oxidation enzyme of Warburg and cannot be dispensed with in normal cellular oxidative processes.³⁵ Vitamin C plays an important role in the redox systems of the cell, probably as a hydrogen acceptor. It has been found that the tissues characterized by high metabolic activity have a high vitamin C content. Such tissues as the interstitial cells of the testes, the anterior and intermediate lobes of the pituitary and the adrenal cortex are the richest sources of vitamin C in the body.³⁶ Ascorbic acid ranks with glutathione as the most active reducing substance known in living tissues.³⁷ Bellows found that sulfhydryls and vitamin C were interchangeable in the oxidative-reductive processes of the lens.

In view of the importance of these substances for normal cellular metabolism, it is not surprising that chronic deprivation of them should have considerable effect not only on the organism as a whole but more specifically on the pace makers, the endocrine glands. These organs are so interdependent that a disturbance in one readily affects the others. The effects of such a disturbance can be far reaching. As King³⁸ said of vitamin C,

33 Tilden, E. B., and Miller, E. G., Jr. Response of the Monkey to the Withdrawal of Vitamin A from the Diet, *J. Nutrition* **3**:121, 1930.

33a Verzar, F. Adrenal Cortex and Intestinal Absorption, *Am. J. Digest. Dis. & Nutrition* **4**:545, 1937.

34 Cowgill, G. R. Physiology of Vitamin B₁, *J. A. M. A.* **110**:805 (March 12) 1938. Peters, R. A. Biochemical Lesion in Vitamin B₁ Deficiency. Application of Modern Biochemical Analysis in Its Diagnosis, *Lancet* **1**:1161, 1936.

35 Mathews, A. P. Vitamins, Minerals and Hormones, Baltimore, William Wood & Company, 1937. Hogan.^{23b}

36 Biskind, G. R., and Glick, D. Studies in Histochemistry. Vitamin C in Testes in Relation to Anatomic and to Functional Changes, *Arch. Path.* **23**:363 (March) 1937.

37. Hopkins, F. G., and Morgan, E. J. Some Relations Between Ascorbic Acid and Glutathione, *Biochem. J.* **30**:1446, 1936.

38 King, C. G. Vitamin C, Ascorbic Acid, *Physiol. Rev.* **16**:238, 1936.

a disturbance in the respiratory enzyme systems in the pituitary gland or the corpus luteum, resulting from slight vitamin deficiency may result in physiological disturbances in the [body] which would be difficult to correlate directly with the primary nutritional disturbance

This statement is just as applicable to the other deficiencies discussed

In view of the far-reaching effects on growth and maturation of even slight deficiencies, the pathologic changes in cases 1 and 2 are more readily understood. The prepubertal appearance of the testes and the lack of maturation, with total absence of spermatogenesis, in 17 year old boys are similar to findings in malnutrition and deficiency states. The basophilic hyperplasia of the pituitary in case 2 is similar to that in rats deficient in vitamins A and E and implies a compensatory reaction to partial castration.

Despite the importance of nutritional deficiencies in the production of secondary infantilism, they are not the only etiologic agents. Secondary endocrine disturbances may be found when no vitamin deficiency is demonstrable and cannot always be correlated with disturbances in growth.^{5a} Such manifestations of endocrine dysfunction are present in chronic diseases when there is considerable variance in the nature of the metabolic upset. Such ailments as chronic heart disease, biliary cirrhosis, hemolytic jaundice, diabetes mellitus and chronic disorders of the gastrointestinal tract disturb the metabolism of the organism in different fashions. Nevertheless, they may all be accompanied or followed by secondary infantilism. It seems, therefore, that any long-continued disturbance of normal metabolic processes taking place during maturation and development may result in secondary infantilism.

SUMMARY

Three cases of infantilism associated with chronic ulcerative colitis are presented. There seems to be no mention of this association in the literature. Further reports of cases are desirable to establish the incidence.

The processes of nutritional deficiencies in the chronic diarrheas are pointed out, and their role in the production of secondary infantilism is discussed.

The role of other metabolic disturbances in chronic diseases is mentioned.

RECURRING ENCEPHALOMENINGORADICULITIS WITH FIBROMYOSITIS FOLLOWING POLIOMYELITIS

A BACTERIOLOGIC STUDY OF SIXTY-FOUR CASES

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It is the purpose of this paper to describe the methods used and to record the results obtained in a study made in July 1937 of 64 cases (in most of which the patients were nurses) of a strange recurring infection, well designated, according to the tissues chiefly affected, as encephalomeningoradiculitis and fibromyositis

In most instances the illness began during an epidemic of poliomyelitis in 1934, in others it began during lesser outbreaks in 1935 and 1936. Acute anterior poliomyelitis was the original diagnosis in most of the cases. The original attack, although usually atypical,¹ was probably referable to the virus of poliomyelitis as well as to the streptococcus.² The virus was demonstrated in the nasopharynxes of all persons by Paul, Trask and Webster³ and in the spinal cord at autopsy by Kessel, Hoyt and Fisk⁴ as well as Rosenow, Heilman and Pettet.⁵ Streptococci were isolated consistently from the nasopharynx, spinal fluid and spinal cord by Rosenow, Heilman and Pettet. Recovery from the primary attack in many instances was sufficient to permit the patients to return to work for from three weeks

From the Division of Experimental Bacteriology, the Mayo Foundation

1 Hart, T M, and Luck, J V. Orthopedic Aspect of the Los Angeles County 1934 Poliomyelitis Epidemic, *Am J Pub Health* **24**:1224-1228 (Oct) 1934

2 Rosenow, E C. The Relation of Streptococci to the Viruses of Poliomyelitis and Encephalitis. Preliminary Report, *Proc Staff Meet, Mayo Clin* **10** 410-414 (June 26) 1935

3 Paul, J R, Trask, J D, and Webster, L T. Isolation of Poliomyelitis Virus from the Nasopharynx, *J Exper Med* **62** 245-257 (Aug) 1935

4 Kessel, F J, Hoyt, A S, and Fisk, R T. Use of Serum and the Routine and Experimental Laboratory Findings in the 1934 Poliomyelitis Epidemic, *Am J Pub Health* **24** 1215-1223 (Oct) 1934

5 Rosenow, E C, Heilman, F R, and Pettet, C H. Observations on the Epidemic of Polio-Encephalitis in Los Angeles, 1934, *Proc Staff Meet, Mayo Clin* **9** 443-451 (July 25) 1934

to three months, at the end of which time increasing weakness, fatigability, pain in muscles and attacks of recurring headaches forced them to bed despite every known treatment

CLINICAL OBSERVATIONS

Most of the patients having severe forms of the disease at the time of this study were hospitalized. They had received every possible care. On inquiry, it was learned that the exacerbations in many of the patients studied who were residing in the same hospital had occurred almost simultaneously. The attacks were characterized by severe headaches, which often were continuous for weeks and were associated in varying degree and frequency with low grade fever, projectile vomiting, occasional diarrhea, transient diplopia, blurred vision, dizziness, incoordination, photophobia, pain behind the eyeballs, deep-seated pain in the back and extremities, extreme nervous irritability, sleeplessness, emotional instability, severe mental depression and muscular weakness and tenderness.

Extreme dysmenorrhea was a common complaint. Sclerotic, cystic ovaries were found and in some cases were removed by operation. Retention of urine caused by paresis of the bladder or stricture of the ureters, with resulting infections, occurred in some cases and was commonly relieved by the use of retention catheters and by ureteral catheterization. Other complications included long-continued superficial hyperesthesias of the skin, deep muscular and musculotendinous tenderness, pain and tenderness of the rheumatic type in the heels and wrists and painful joints. A history of recurring attacks of urticaria was elicited from 17 of 53 patients. A striking finding in several instances was fibrous ankylosis of the interphalangeal joints of the hands of such severity that the fingers could not be clenched into a fist.

Certain patients had reacted favorably to care by well trained physical therapists, who had applied local heat and massage and had tried individually supervised exercises. Many patients who had experienced mild attacks had returned to part time or full time duty. A considerable number reported that they had fared well with rest, without physical therapy. Hyperactivity rather than diminution or absence of tendon reflexes was the rule, even in the presence of widespread muscular weakness without proportionate atrophy. Muscles of good size were apparently present and could be caused to contract voluntarily but without much power. Tonic and clonic spasms of muscles were common, some muscles even requiring application of a cast for their control. Paroxysmal tachycardia, with rapid, thready pulse, attacks of pseudoangina and recurring attacks of mild sore throat and diarrhea were not uncommon. Most striking of all observations concerning

muscular involvement were the universal lack of muscular endurance, the variability of response and strength and the early tiring and exacerbations which were often directly attributable to mental and physical overexertion. The muscles of the abdomen and of the region of the hip were most often affected. Localized paralysis and wasting of muscle groups, such as are seen in typical infantile paralysis, were uncommon.

In short, there was apparent almost every conceivable combination of symptoms and findings referable to purely functional or mental disturbances, as generally understood, and also to physical diseases, yet almost none of these was typical of any well known disease. Clinically the condition in some of the cases resembled the infectious neuronitis described by Kennedy⁶ and the "myeloradiculitis" described by Strauss and Rabiner.⁷ Wilson and Walker⁸ reported that the early observations during and soon after the epidemic of 1934 were different from those which characterize typical epidemic poliomyelitis. Unique were the high incidence (about 10 per cent) of poliomyelitis among nurses and physicians while they were caring for the sick and the large number of persons who had recurring exacerbations. The usual sex incidence of poliomyelitis was reversed among patients who had recurring attacks, the number of females afflicted being three times that of males. Older children and young adults were stricken chiefly. This was true also during the large outbreak in Denmark in 1934. The late manifestations of the disease, however, did not appear during the latter epidemic.⁹

Rosenow, Heilman and Pettet⁵ also stressed the atypical character of the primary disease and reported results observed in animals inoculated with streptococci isolated consistently from the nasopharynxes, spinal fluid, brains and spinal cords of patients. These results differed from those usually obtained in similar studies of typical epidemic poliomyelitis. The incidence in the inoculated animals of flaccid paralysis like that observed in patients at the time of the epidemic was not so high, but evidences of pain were more numerous and the incidence of muscular spasms and lesions of the muscles was higher.

6 Kennedy, F. Infective Neuronitis, *Arch Neurol & Psychiat* **2** 621-627 (Dec) 1919.

7 Strauss, I., and Rabiner, A. M. Myeloradiculitis. A Clinical Syndrome, with a Report of Seven Cases, *Arch Neurol & Psychiat* **23** 240-256 (Feb) 1930.

8 Wilson, J. C., and Walker, P. J. Acute Anterior Poliomyelitis. Orthopedic Aspects of the California Epidemic of 1934, *Arch Int Med* **57** 477-482 (March) 1936.

9 Jensen, C. The 1934 Epidemic of Poliomyelitis in Denmark. Preliminary Report on the Epidemiology and Clinical Features and Convalescent Serum Therapy, *Proc Roy Soc Med* **28** 1007-1026 (June) 1935.

METHODS AND SCOPE OF STUDY

On the basis of these observations it was thought that a bacteriologic study by methods which I have previously described and by means of serologic tests recently developed might throw light on the causation of this complex syndrome. Cultures in dextrose-brain broth and other mediums were made from material obtained by swabbing the nasopharynx and the uterine cervix, from the urine and feces, from the blood and cerebrospinal fluid and from excised specimens of affected muscles and ovaries. Animals—mice, rabbits and monkeys—were given injections of the organisms thus freshly isolated. The cataphoretic velocity of the streptococci was determined by methods previously described, without knowledge of the condition of the patient or of whether the culture tested was obtained from controls.¹⁰ Cutaneous, precipitation and agglutination tests were made with

10 I am aware of the skepticism of some regarding the value of cataphoretic studies on streptococci. By virtue of strict attention to technical details my associates and I have obtained consistent results in such a variety of diseases as to convince us of the value of such studies. Others have reported similar results.⁶ The differences in the results obtained by different workers are largely attributable to differences in technic—to the small number of strains tested, to the time of the study, to the type of mediums used and to faults of interpretation. It has been shown that seasonal changes occur in the cataphoretic velocity of streptococci (Rosenow, E. C., and Jensen, L. B. *Cataphoretic Velocity of Streptococci Isolated in Cases of Encephalitis and of Other Diseases of the Nervous System*, *J. Infect. Dis.* **52** 167-184, 1933). The determination of the cataphoretic time and velocity of streptococci has significance almost never, except when the strain used has been freshly isolated (Rosenow, E. C., and Davis, C. H. *The Bacteriology and Experimental Production of Ovaritis*, *J. A. M. A.* **66** 1175-1180 [April 15] 1916). We have found that mediums to which brain tissue has been added before autoclaving, such as dextrose-brain broth, are especially favorable to the isolation of pathogenic streptococci. This point has been corroborated by Burdon and his associates (Burdon, K. L., Thurston, E. W., Varnev, P. L., and Bronfenbrenner, J. *The Etiologic Significance of Streptococci in Epidemic Encephalitis. I. Incidence of Streptococci in Cultures from Patients with Encephalitis in St. Louis and from Normal Controls, and Characteristics of the Various Strains Isolated*, *Arch. Int. Med.* **58** 285-308 [Aug.] 1936, *II. Experiments with Animals and Conclusions*, *ibid.* **58** 469-494 [Sept.] 1936). Such mediums are also favorable to the maintenance of elective localizing power and (concomitantly) characteristic cataphoretic velocity (Rosenow, E. C., and Ashby, W. *Focal Infection and Elective Localization in the Etiology of Myositis*, *ibid.* **28** 274-311 [Sept.] 1921). In our extensive experience with primary dextrose-brain broth cultures of material from the nasopharynges of persons suffering from encephalitis or other epidemic diseases, my associates and I have never found that long chains of streptococci or contaminating organisms were present in sufficient number to alter perceptibly the distribution curves of cataphoretic time velocity, which these investigators suggest as possible sources of error. Moreover, I have shown that the distribution curves of cataphoretic time and velocity of the streptococci which grew in the primary culture in dextrose-brain broth were not only characteristic of, but were nearly identical with, the distribution curves of the streptococci that had grown not in the culture mediums but in the nasopharynx or in foci of infection elsewhere and that were timed directly. The discrepancies, or what

serums obtained from patients and with different antistreptococcic serums from immunized horses

Nearly all material was inoculated on blood agar plates for detection of aerobes and into deep tubes of dextrose-brain broth for the isolation of partial oxygen tension or anaerobic organisms. The amount of inoculum varied greatly for different tubes of medium. In some instances the spinal fluid was incubated after layering with sterilized linseed oil. Cultures were also made by dipping swabs coated with coagulated horse serum into the spinal fluid and incubating these and by layering the spinal fluid over Löffler's blood serum slants. Blood was drawn from the patient in a sterile manner and placed in vacuum vials, where it was allowed to clot. The serum was removed, and the partially macerated clot was transferred with sterile precautionary measures to dextrose-brain broth.

Dextrose-brain broth, the medium chiefly used, was freshly prepared by adding pieces of brain from calves slaughtered on the same day to an infusion or extract broth to which 0.2 per cent dextrose and Andrade's indicator were added. The reaction was brought to a pH of 7, and the medium was placed in columns of from 10 to 12 cm in height in deep tubes (20 by 1.5 cm). Pieces of brain representing a volume of from 2 to 3 cc for each tube were added before autoclaving.

Burdon, Thurston, Varney and Bronfenbrenner interpreted as such, in the distribution curves of cataphoretic velocity of the streptococci isolated in their and our studies of the St. Louis epidemic of encephalitis are explicable on the basis of their use of strains too long after isolation and also on the basis of the difference in time of study. Our study was made during hot weather (summer), at the height of the epidemic, theirs was conducted during cooler weather (autumn), after the epidemic had largely subsided. Their average distribution curve of cataphoretic velocity of the streptococci freshly isolated in cases of encephalitis stacked at nearly the "neurotropic" cataphoretic time of 2 to 2.5 seconds, while that of the strains freshly isolated from the nasopharynges of well controls stacked markedly at nearly the "pharyngotropic" time of 3.5 seconds. The three groups of strains that had been cultivated for some time on artificial mediums likewise stacked heavily at nearly 3.5 seconds. Their results approximated precisely what one would expect. The curve of the streptococci freshly isolated in the cases of encephalitis approached the "neurotropic" type at nearly the cataphoretic time of 2 seconds, instead of mainly at 4 seconds. The former type in our studies was obtained especially at the onset of acute attacks, the latter, at a later time, during attacks. Both types have been shown to have neurotropic virulence. All of the other four groups of strains approximated the "pharyngotropic" type at nearly 3.5 seconds, which is obtained in streptococci freshly isolated from the nasopharynges of persons suffering from the common or autumnal cold and to a lesser degree in streptococci from the nasopharynges of well persons in autumn during epidemics of colds (Rosenow and Jensen). Shifts in cataphoretic velocity of streptococci according to seasons such as these, unsuspectingly determined by Burdon and his associates, have been repeatedly noted of streptococci freshly isolated from the nasopharynges of well persons (Rosenow and Jensen) and simultaneously, or nearly so, of streptococci in cases of encephalitis and other diseases as kept in dextrose-brain broth cultures in the laboratory. By the strictest attention to technical details and by having the operator make readings of cultures without knowledge of the condition of the patient or of whether the organisms were obtained from controls, we have again obtained by our method, as will be shown, information of importance as regards the nature of the strains from different patients in the group under study.

at 20 pounds (9.1 Kg) of pressure for twenty minutes. In some instances the dextrose-brain broth was placed in hermetically sealed bottles of from 15 to 120 cc capacity. The inoculated mediums were incubated at 35 C (95 F).

Mice were given injections of cultures or direct injections of spinal fluid or other material, 0.03 cc intracerebrally and (usually) 2.5 cc intraperitoneally. Rabbits and monkeys were inoculated intracerebrally and/or intravenously with cultures or directly with material obtained from patients and other sources. The dose varied between wide limits, depending on the nature of the material under study. Routinely, 0.1 cc of a suspension of swabbings from the nasopharynx or from the uterine cervix in 2 cc of saline solution was injected intracerebrally, and 0.1 cc of a 1:200 or 1:1,000 dilution of the dextrose-brain broth culture and 0.5 cc of the undiluted culture for each 100 Gm of body weight were injected intravenously into rabbits and monkeys. In special instances the doses were much less, sometimes a thousandfold less, yet positive results were obtained. The animals were observed repeatedly every day for symptoms and were examined for lesions as soon after death as was possible. Those that survived were etherized to death within from three to fourteen days after inoculation. The excised muscles, ovaries and tissues of animals were fixed in solution of formaldehyde U. S. P. diluted 1:10, and paraffin sections were stained with hematoxylin and eosin and by the Gram method. In the latter procedure, however, no counterstain was used, and decolorization was carried out only to a fair blue instead of to the end point.

Precipitation tests¹¹ were made with saline extracts of nasopharyngeal swabbings and with the serums of patients. These were layered in small tubes over the serums of horses hyperimmunized with streptococci isolated during studies of encephalitis, poliomyelitis, arthritis and ulcerative colitis. As controls, the extracts and serums from patients were also layered over the antisera after absorption of the latter with the homologous streptococci. Clouding at the interface with the unabsorbed antiserum and the absence of clouding or clouding of lesser degree with the absorbed serum indicated the presence in the throat or serum of the patient of a streptococcic antigen immunologically related to the streptococci with which the reacting antiserum had been prepared.

Cutaneous tests were made by injecting intradermally 0.05 cc of a 10 per cent solution in saline of the euglobulin (antibody) fraction of the antiserum. The antisera used were those of horses hyperimmunized to different streptococci and those (diluted 1:10) of persons convalescing from acute exacerbations of the disease. An erythematous-edematous reaction within ten minutes after injection of the antiserum or convalescent serum indicated the presence in the skin or blood of an antigen immunologically related to the streptococci with which the reacting serum had been prepared¹¹ and to the infective streptococci in the patient from whom the convalescent serum (antibody) had been obtained. In every case the estimation of the degree of reaction was concurred in by two or more observers.

Agglutination tests were made with strains of the streptococci isolated from the nasopharynx, stools, uterine cervix, urine, blood, spinal fluid and muscles. Agglutination experiments were done according to a special technic which we have found essential to the securing of evidence of the presence of streptococci.

11 Heilman, F. R., and Rosenow, E. C. Newer Methods of Study and Treatment of Chronic Streptococcal Disease, *Proc. Staff Meet., Mayo Clin.* **12**: 252-256 (April 21) 1937.

agglutinins in the serums of patients with chronic streptococcic diseases and patients with acute poliomyelitis and encephalitis. The streptococci freshly isolated in dextrose-brain broth were centrifuged, the supernatant broth was poured off, the organisms were suspended in small amounts of glycerin (2 parts) and 25 per cent salt solution (1 part), and from this dense suspension dilutions were made to the density of a dextrose-brain broth culture. These diluted suspensions were then mixed in 0.2 cc amounts with 0.2 cc amounts of the respective dilutions of serum in Wassermann tubes. The mixtures were incubated at 50 C (122 F) for eighteen hours and then read.¹²

12 Pertinent to the problem under consideration, I wish here to point out wherein lay the inability of some investigators to corroborate the results obtained in our studies on streptococci in encephalitis. By the use of this method of agglutination we found, contrary to the results obtained by Burdon, Thurston, Varney and Bronfenbrenner, that the serum of patients convalescing from encephalitis in St. Louis agglutinated more strongly and in much higher dilution the streptococci isolated consistently from the nasopharynx, spinal fluid and brain in our study made during the height of that epidemic than did the serum of well controls. Considering the confirmatory results obtained in other respects, it is unfortunate that the aforementioned investigators tested the agglutinating power of convalescent serum on strains of streptococci after those strains had been cultivated on artificial mediums for some time instead of on freshly isolated strains, making suspensions directly from cultures instead of from dense glycerin-saline solution suspensions, incubating the mixtures at 37 C (98.6 F) for only one and a half hours and then placing them in the ice chest overnight instead of incubating them at 50 C (122 F) for eighteen hours. We, also, did not get agglutination when we proceeded under such conditions. Also pertinent to this study is the fact that these investigators seem to have missed the point that animals which after injection of streptococci survived the acute symptoms and later showed manifestations of encephalitis and which succumbed or were anesthetized late almost always exhibited typical perivascular lymphocytic infiltrations in the brain. Burdon, Thurston, Varney and Bronfenbrenner showed photomicrographs only of acute lesions, and, of course, the infiltrating cells to be seen in these were mainly polymorphonuclear leukocytes, a finding which is in accord with the fact that in the very early stages of the disease in the human being these cells are often present in the spinal fluid, sometimes in predominating numbers.

Whether the streptococcus played the role of an important secondary invader in that epidemic, as was concluded by them, or whether the streptococcus played the primary role and the virus the secondary one, it is impossible to decide on the basis of published data now available. A forthcoming report will contain important information on the relation of the streptococcus to the virus of encephalitis.

McKinley's report (McKinley, E. B. Failure to Confirm Rosenow's Work on Encephalitis in Its Relation to Green Streptococcus, *Proc. Soc. Exper. Biol. & Med.* **27** 436-440 [Feb.] 1930) I have disregarded because he injected, as far as I can tell, into only 2 rabbits streptococci from the nasopharynxes of 25 well persons in Puerto Rico and only 1 patient with encephalitis. However, since Burdon, Thurston, Varney and Bronfenbrenner attach significance to his work, I am impelled to state that if he had injected highly diluted cultures (as high as 1:1,000,000), as we did, instead of only our maximal dose (0.2 cc)

RESULTS OF CULTURES AND OF SEROLOGIC STUDIES

Blood agar platings directly from swabbings of the nasopharynx and the uterine cervix, or from the primary growth in dextrose-brain broth, yielded uniformly a large number of green-producing streptococci or indifferent colonies of streptococci and almost never hemolytic streptococci. The primary cultures in dextrose-brain broth uniformly yielded pure or almost pure cultures of streptococci (fig 1 *A*). Green-producing streptococci were repeatedly isolated in large numbers from specimens of stools obtained during exacerbations of symptoms. The results of cultivation of specimens of the blood, spinal fluid, muscles, ovary and catheterized urine are summarized in table 1.

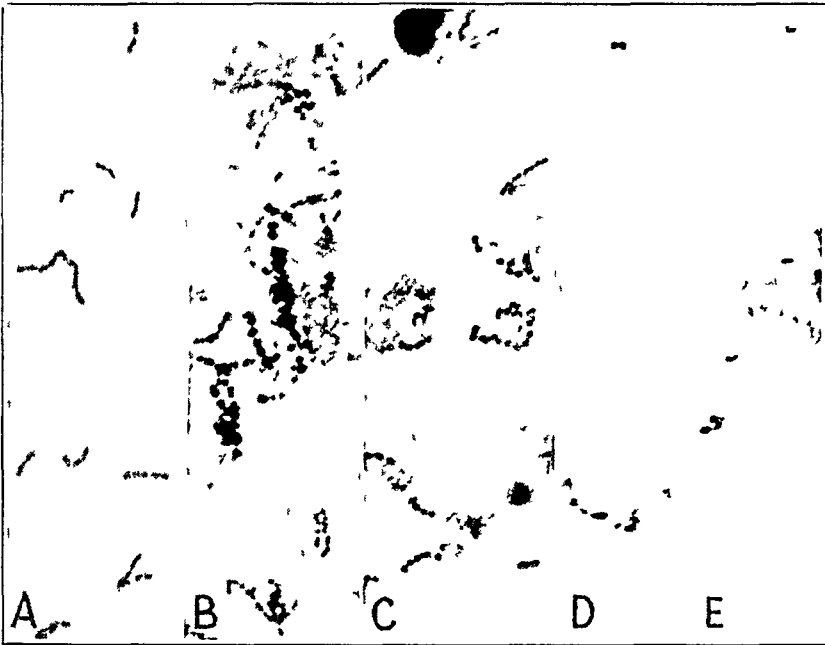


Fig 1—Streptococci as isolated in dextrose-brain broth, from (*A*) nasopharyngeal mucus, (*B*) blood, (*C*) spinal fluid, (*D*) cystic fluid from ovary and (*E*) excised muscle. Rosenow-Gram stain, $\times 1,000$.

of the suspension of material from the nasopharynx and tonsils, he would no doubt have obtained not only the early acute manifestations of meningoencephalitis but the late more typical symptoms and lesions, as have we. Differentiation by the agglutination reaction of green-producing streptococci from throats of well persons and persons with encephalitis or poliomyelitis was possible only in dilutions of the antisera which I sent him above those which he used. The demonstration in the throats of well persons of green-producing streptococci which have early effects in rabbits like those of the streptococci in encephalitis does not disprove the etiologic importance of the streptococcus in encephalitis any more than the demonstration of the diphtheria bacillus in the throats of well persons disproves the etiologic importance of the diphtheria bacillus in diphtheria.

Cultures of blood clot were made in freshly prepared dextrose-brain broth in 64 cases. In Glendale the cultures were made within four hours and in Rochester within forty-eight hours after drawing the blood. The organisms obtained are represented in figure 1. All the cultures made in Rochester remained sterile, while those made at once in Glendale yielded streptococci (fig 1 B) roughly in proportion to the severity of the symptoms in the patients. Only rarely were streptococci isolated from healthy exposed persons, and at Rochester they were never grown from blood of nonexposed persons. Thus, as is shown in table 1, streptococci were isolated from only 3 (13 per cent) of 24 patients with mild symptoms, from 12 (63 per cent) of 19 patients with severe symptoms at the time the blood was drawn and from only 1 (5 per cent) of 21

TABLE 1—*Results of Culture of Materials Obtained in Patients with Recurring Encephalomeningoradiculitis and Fibromyositis and from Others*

Material Cultured	Source	Total Number	Number with Cultures Positive for Streptococci	Percentage* with Cultures Positive for Streptococci
Blood	Patients with given type of involvement			
	Severe	19	12	63
	Mild	24	3	13
	Recovered	21	1	5
	Exposed persons	15	5	33
	Control nurses			
	Glendale, Calif	18	0	0
	Rochester, Minn	45	0	0
Spinal fluid	Patients with severe involvement	14	13	93
Excised muscles		5	4	80
Ovary		1	1	100
Catheterized urine		15	8	53

* Percentages are given to the nearest whole number

persons who had returned to work. Streptococci were isolated from the blood of 5 (33 per cent) of 15 nurses and physical therapists who were in close contact with the disease, some of whom complained of undue fatigability and other symptoms. In no instance were streptococci isolated from the blood of three groups of nonexposed nurses, one group consisting of 18 residing in the epidemic zone, the others consisting of 27 and 18, respectively, residing outside of the epidemic zone. Through the assistance of Dr F E Poole, of Glendale, 1 or 2 specimens of spinal fluid obtained from each of 14 patients having active infections were made available. The cell count was extremely low in all specimens, 9 disclosed the presence of one cell per cubic millimeter, 8 showed two cells, 2 showed three cells and 2 showed four cells. Extremely pleomorphic gram-positive to gram-negative diplostreptococci were isolated from the spinal fluid of 13 of the 14 patients (fig 1 C). The bacteria

obtained from the spinal fluid did not always grow out as typical streptococci when they were cultivated in artificial mediums, but those from the brains of mice and rabbits that died in from three to eight days after intracerebral inoculation of the atypical cultures and those in specimens of spinal fluid plated directly usually did. Cultures were made of catheterized urine from 15 patients, and 8 of the cultures showed growth of streptococci.

Excised pieces of tender muscle from 5 patients were cultured and examined microscopically. Three of these yielded pure cultures of extremely pleomorphic streptococci (fig 1 *E*). One yielded streptococci with diphtheroid bacilli and micrococci (sometimes all three forms were present in the same chain). One remained sterile, and sections showed no lesions. The 4 specimens yielding streptococci showed irregular staining and degeneration of muscle fibers, fibrosis, and perivascular and other infiltration by mononuclear cells and scattered diplococci in or adjacent to the lesions (figs 2 and 3). One cystic ovary (from a patient who suffered almost intolerably at the menstrual period) became available for study. Extremely pleomorphic streptococci (fig 1 *D*), especially resembling those from the spinal fluid and muscles (fig 1 *C* and *E*), were isolated in dextrose-brain broth from the cystic fluid of this ovary, from pieces and also from emulsions of the tissue. Sections disclosed the presence of advanced fibrosis, cellular infiltration in the walls of the cysts, a few diplococci in the walls of the cysts and large numbers of diplococci in the coagulated albuminous film in the lumens of the cysts (fig 4).

The incidence of positive reactions to precipitation tests, indicating the presence of an antigen related to the streptococci with which the reacting antiserum was prepared (table 2), was highest with the nasopharyngeal extracts and the serums from patients having active infections, next highest with those from exposed persons and lowest with those from nonexposed persons, when these extracts and serums were layered over antisera prepared with streptococci isolated respectively from persons with chronic encephalitis (neurotropic strains) and from persons with chronic infectious arthritis (arthrotropic strains).

The immediate erythematous reactions¹¹ to the different antisera (indicating the presence of antigen in the skin related to the streptococci with which the reacting antisera were prepared) varied greatly in different patients. The greatest reaction was usually that to an antiserum prepared with streptococci isolated from a disease in which the symptoms were most nearly like those of the patient at the time of the test. Thus if neuritic pains, so common during the epidemic (radiculitis), were marked, the greatest erythematous reaction was that to the antiserum prepared from strains isolated during studies of the Los

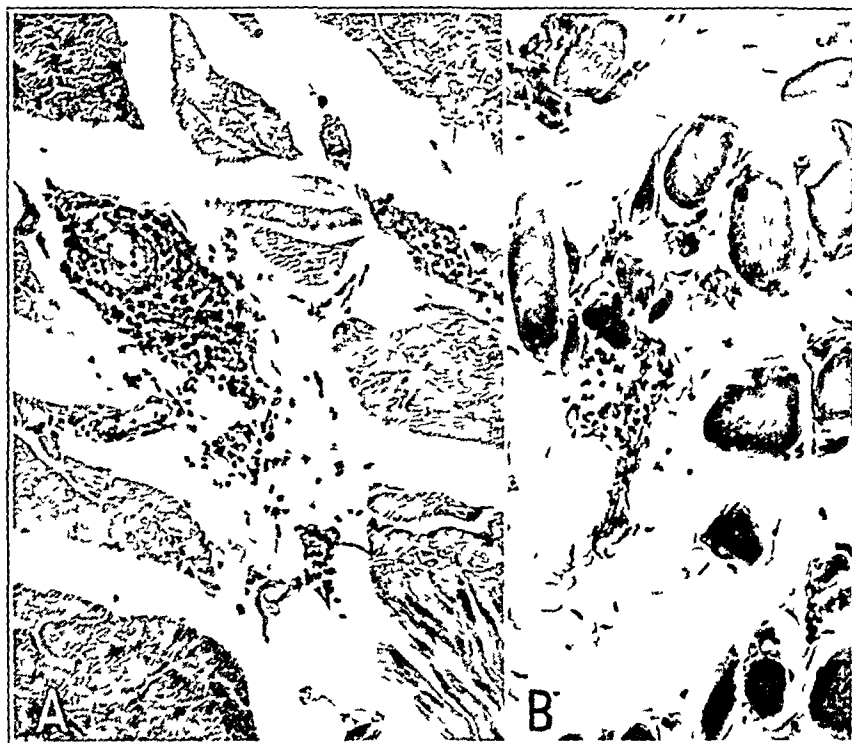


Fig 2—Edema and perivascular and interstitial cellular infiltration of excised muscles of 2 patients who had severe pain referable to muscles. Hematoxylin and eosin stain, $\times 150$

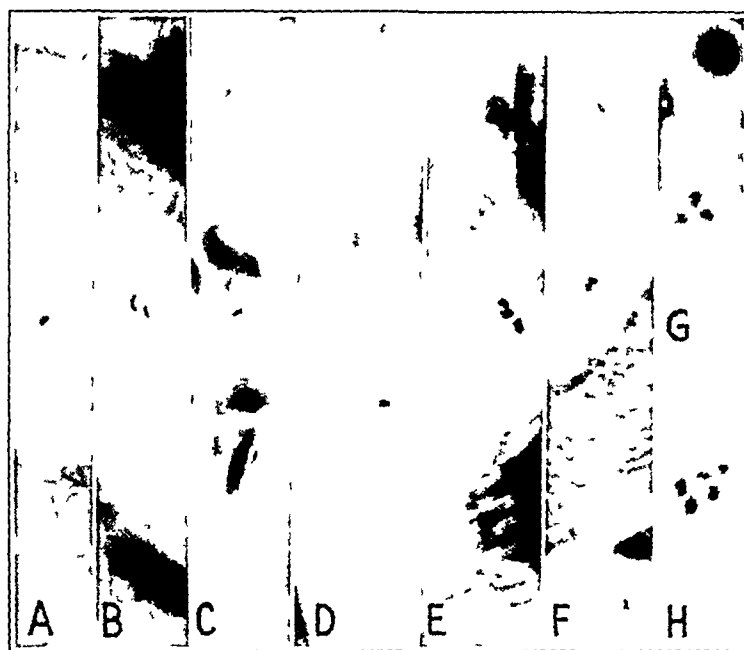


Fig 3—Pleomorphic diplococci in the lesions of muscles shown in figure 2. Rosenow-Gram stain, $\times 1,000$

Angeles epidemic of poliomyelitis. If, however, muscular or rheumatic symptoms of myositis with or without arthritis predominated (which was the rule), the greatest erythematous reaction was observed when the antiserum prepared with streptococci isolated in studies of arthritis was used. If involvement of muscles associated with undue fatigability was especially marked, the greatest erythematous reaction was that to the antiserum prepared with streptococci from patients with myasthenia gravis. The average reactions of all the groups tested with the different antisera are given in table 3.

The reason for the relatively high incidence of precipitation reactions with the polioencephalitis and arthritis antisera (table 2) and the

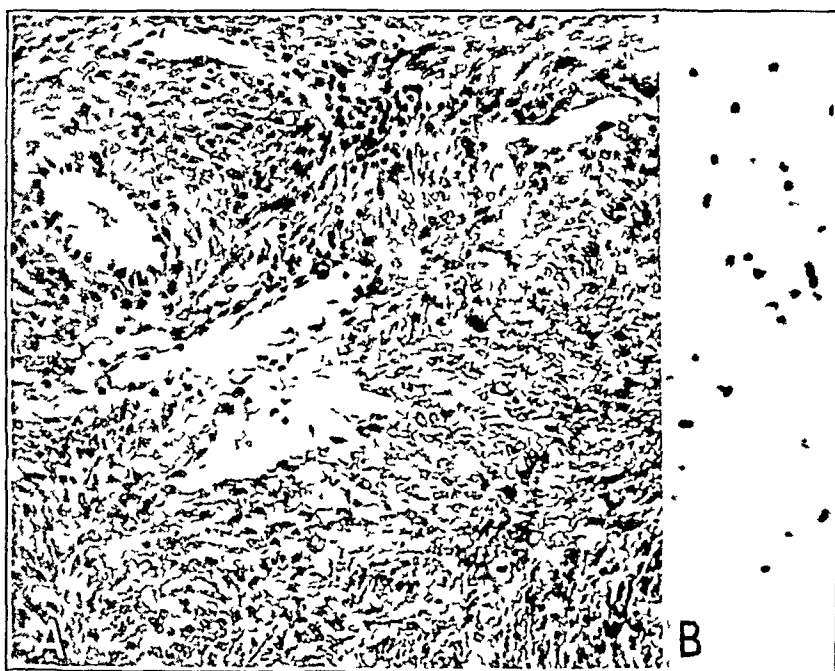


Fig 4—*A*, edema, degeneration, fibrosis and cellular infiltration and (*B*) diplococci in the ovary removed surgically from a patient who had almost intolerable pain during menstruation (*A*, hematoxylin and eosin stain, $\times 150$, *B*, Rosenow-Gram stain, $\times 1,000$)

serums from the group of nurses at hospital A (Rochester) used as antigen and of the relatively marked cutaneous reactions (table 3) is not entirely clear. It is possible that streptococci similar to those isolated during our study of the cases in 1934, which we isolated from the drinking water of the group of nurses at hospital A (Rochester) at the time of the study, might have been responsible. The streptococci isolated produced lesions of muscles, fascia and nerve sheaths after intracerebral and intravenous injection. Several nurses had mild symptoms resembling those arising from neurofibromyositis shortly before or at the time,

TABLE 2—*Precipitation Reactions Between Antistreptococcic Serums and*
(1) Cleared Saline Extracts of Nasopharyngeal Swabbings
and (2) the Serums of Patients

Source of Antigen	Groups	Number	Percentage* with Positive Reactions to Serums from Horses Hyperimmunized with Streptococci from Patients Ill with					Control Percentage with Reactions to Normal Horse Serum (1/10)
			Chronic Encephalitis	Acute Encephalitis (St. Louis)	Polioencephalitis (Los Angeles)	Chronic Infectious Arthritis	Ulcerative Colitis	
Nasopharynx	Patients	55	49	18	11	43	18	2
	Exposed persons	41	19	10	5	24	10	2
	Nonexposed persons							
	Glendale, Calif	17	6	0	0	19	0	0
	Rochester, Minn	47	6	6	4	4	6	0
Serum	Patients	62	55	21	16	29	15	0
	Exposed persons	35	54	6	17	11	14	0
	Nonexposed persons							
	Nurses, Glendale, Calif	18	44	6	22	17	0	0
	Nurses, Hospital A, Rochester, Minn	26	27	8	8	15	0	0
	Nurses, Hospital B, Rochester, Minn	18	6	0	0	6	0	0

* Percentages are given to the nearest whole number

TABLE 3—*Results of Intradermal Tests with the Englobulin (Bacterial Antibody)*
Fractions of Serums of Horses Hyperimmunized with
Different Types of Streptococci

Group	Number	Average Reaction (Sq. Cm.) to Antibodies in Serums Prepared with Streptococci from Patients Ill with							Control Average Reaction to Normal Horse Serum (1/10)
		Polioencephalitis (Los Angeles)	Typical Polioencephalitis	Chronic Encephalitis	Acute Encephalitis (St. Louis)	Chronic Infectious Arthritis	Ulcerative Colitis	Myasthenia Gravis	
Patients with active infection	40	75	66	30	64	130	34	66	16
Convalescent patients									
Severe symptoms*	29	56	48	20	24	103	33	38	13
Mild symptoms*	46	37	35	13	23	66	18	19	14
Exposed persons (nurses and physical therapists)	37	37	33	12	30	75	19	27	12
Nonexposed persons									
Nurses and other hospital personnel, Glendale and Los Angeles, Calif	39	17	14	123	15	69	10	21	06
Nurses, Hospital A, Rochester, Minn	27	48		10		44		14	16
Nurses, Hospital B, Rochester, Minn	18	28		07		21	17	07	08

* At the time of the test

and similar cultures of the drinking water of the group of control nurses at hospital B (Rochester), among whom the incidence of precipitation and cutaneous reactions was much lower, failed to reveal streptococci. Because of the great differences as to the chief complaint in the different cases, the average size of the area of reaction does not adequately express how specific or diagnostic these cutaneous reactions were. The degree of reaction to the "homologous" antiserum was usually directly proportional to the severity of symptoms. Similar results were obtained after intradermal injection of the serum (antibody) obtained from patients during convalescence from acute exacerbations of the disease. Thus, in 10 patients having acute attacks the average area of erythematous reaction to the serum obtained from a patient recovering from an exacerbation was 9.7 sq cm, in 17 convalescent patients it was 4.8 sq cm and in 27 healthy exposed persons it was 3.4 sq cm. To the serum of a well

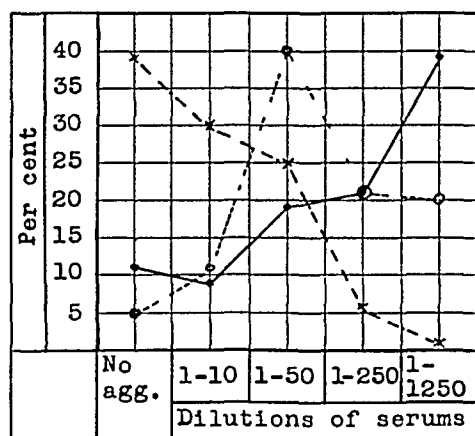


Fig 5—Absence and end point of agglutination of the streptococci by the serums of 50 patients in 133 tests (solid line) of 21 exposed persons in 41 tests (dotted line) and of 26 nonexposed persons in 88 tests (dot and dash line)

person of the same age and sex the areas of reaction were 2.3, 1.0 and 1.8 sq cm, respectively, in the same three groups of subjects.

The agglutinating power of individual serums and of pools of six serums from patients, exposed persons and nonexposed persons over separate strains and pooled strains of streptococci was determined under comparable conditions. The results of the agglutination experiments are summarized graphically in figure 5. The incidence of nonagglutination was much higher when serums from nonexposed persons were used than when serums from patients and exposed persons were used. The end point of agglutination became progressively higher with increasing dilutions of the serum from patients, less so with the serum from exposed persons and progressively lower with the serum from nonexposed persons. In addition, the serums from these patients especially agglutinated

the pooled suspensions of streptococci from patients with arthritis, neuromyositis or myasthenia gravis, suspected material to which the patients were exposed and, to a lesser degree the streptococci isolated during the epidemic. These serums did not agglutinate the streptococci obtained from patients with acute encephalitis.

The average distribution curves of cataphoretic velocity of the streptococci obtained from patients and exposed persons, without regard to the cutaneous reactions and according to whether cutaneous reactions occurred to the "arthrotropic" or the different "neurotropic" serums were determined by methods previously described and are summarized in figure 6. It will be seen that the distribution curve of cataphoretic velocity of streptococci isolated from patients and exposed persons without regard to the cutaneous test covered a wide range, with maximal

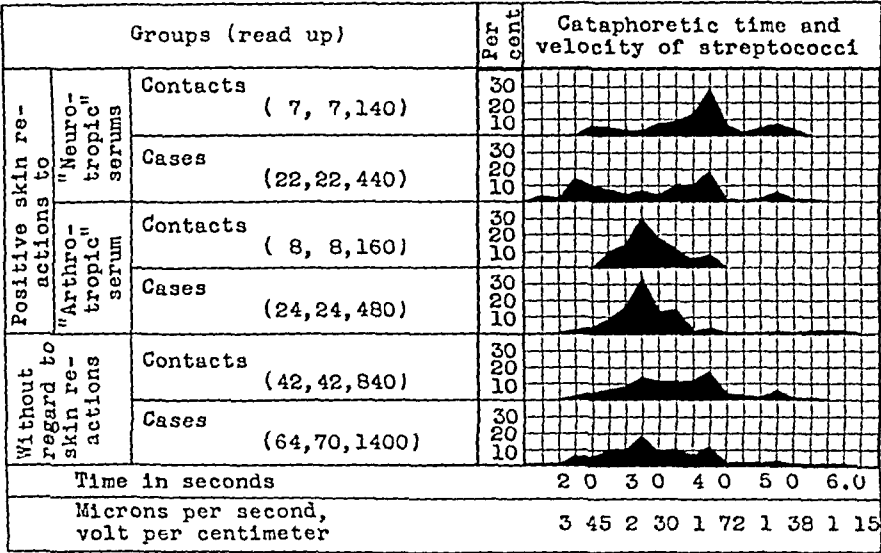


Fig 6—Cataphoretic time and velocity of streptococci isolated from the nasopharyngeal mucus of patients having recurring attacks of encephalomeningoradiculitis and fibromyositis and also from the nasopharyngeal mucus of exposed persons. The figures in parentheses indicate, respectively, the numbers of strains, cultures and streptococci timed in each group.

numbers occurring in the "arthrotropic" and "neurotropic" columns (230, 345 and 172 microns per second, volt per centimeter). The streptococci from the nasopharynxes of patients and exposed persons who reacted strongly in the cutaneous test to the "arthrotropic" serum and whose symptoms at the time were mainly referable to connective tissue and muscle had an "arthrotropic" distribution curve, and the streptococci from persons who reacted strongly to one or more serums prepared with streptococci from persons who had disease of the nervous system and symptoms referable chiefly to the nervous system had a "neurotropic" distribution curve.

RESULTS IN ANIMALS OF INTRACEREBRAL AND INTRAVENOUS INOCULATION OF THE ISOLATED STREPTOCOCCI

Since the condition in most of the patients under study began during the epidemic of atypical poliomyelitis in 1934, I have summarized for comparison the results obtained in experiments with streptococci isolated at that time and the results of similar experiments performed with streptococci isolated from patients suffering three years later from this strange combination of recurring symptoms of encephalomeningo-

TABLE 4—*Mortality, Symptoms and Incidence of Lesions Among Animals Inoculated with the Isolated Streptococci*

Source of Streptococci	Time of Study	Method of Inoculation	Species	Strains	Animals		Animals Showing Given Symptom				Animals Showing Lesions of			
					Inoculated	That Died	Pain	Paralysis	Spasms	Intelligence	Brain and Cord	Dura	Nerve Roots	Muscles and Fascia
Nasopharynx, spinal fluid, brain and cord of patients	1934	IC* or IV†	Rabbit and monkey	13	93	71	19	32	13		34	19	15	16
Nasopharynx, cervix, urine, stool, blood, spinal fluid, muscle and ovary of patients	1937	IO	Rabbit and monkey	23	32	69	50	16	41	41	23	23	23	72
		IV	Rabbit	11	15	60	47	13	20	47	33			80
		IO and IV	Rabbit	9	17	88	30	18	41	41	24	41	60	88
		IC and IV	Monkey	6	6	66	100	33	33	67	33	83	83	100
		Total		39	70	71	49	17	36	44	27	30	49	80
Nasopharynx (well exposed persons)	1937	IO	Rabbit	15	16	50	6	13	6	0	0	6	6	6
Filtrates of nasopharyngeal washings	1937	IO	Rabbit and monkey	10	17	0	0	0	0	0	0	0	0	0

* Intracerebral

† Intravenous

radiculitis and fibromyositis, from exposed persons and from other sources

In the present study the results after injection of the streptococci isolated from the swabbing of the nasopharynx and cervix and from blood, urine, stool, spinal fluid, excised muscles and ovaries were strikingly similar to those obtained in the earlier study. The observations following intracerebral and intravenous injection of streptococci into rabbits and monkeys are summarized in table 4. During the epidemic and three years later the mortality of the animals was consistently high and was always higher than after injection of streptococci from healthy exposed persons. The incidence of the chief symptoms and lesions in

the two groups of experiments paralleled in general and often strikingly, that in the patients from whom the streptococci were obtained. This was true particularly as regards evidence of pain (especially pain referable to the head and muscles), weakness or paralysis, fatigability and spasm of muscles and as regards the incidence of lesions of the brain cord, dura mater, nerve roots, muscles, fascia and ovaries.

Gross lesions of the brain and spinal cords of monkeys on cross section were rare, and microscopically small areas of necrosis and of leukocytic and round cell infiltration (fig 7) with or without diplococci were seen occasionally. Grossly visible diffuse meningitis was not

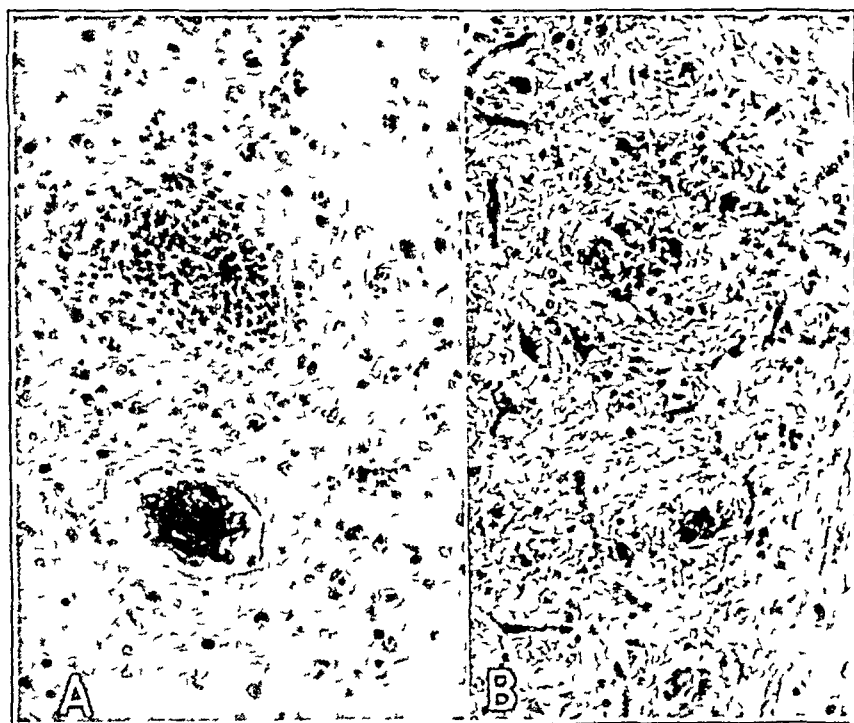


Fig 7—Areas of necrosis and cellular infiltration (A) in the brain and (B) in the medulla of a monkey inoculated five days previously with streptococci from the blood of a patient who had had recurring attacks of severe headache and severe deep-seated pain in the hips and legs. Hematoxylin and eosin stain $\times 150$.

encountered. The dura over the cerebral cortex and the calvarium was often seen to be extremely congested, and the dura covering the lumbar portion of the cord and the cauda, in addition to being congested, was often edematous, hemorrhagic and infiltrated (fig 8). Both anterior and posterior nerve roots, especially in the lumbar region, were often extremely hyperemic, were surrounded by hemorrhage and edema and microscopically were seen to be infiltrated by leukocytes and round cells (fig 9).

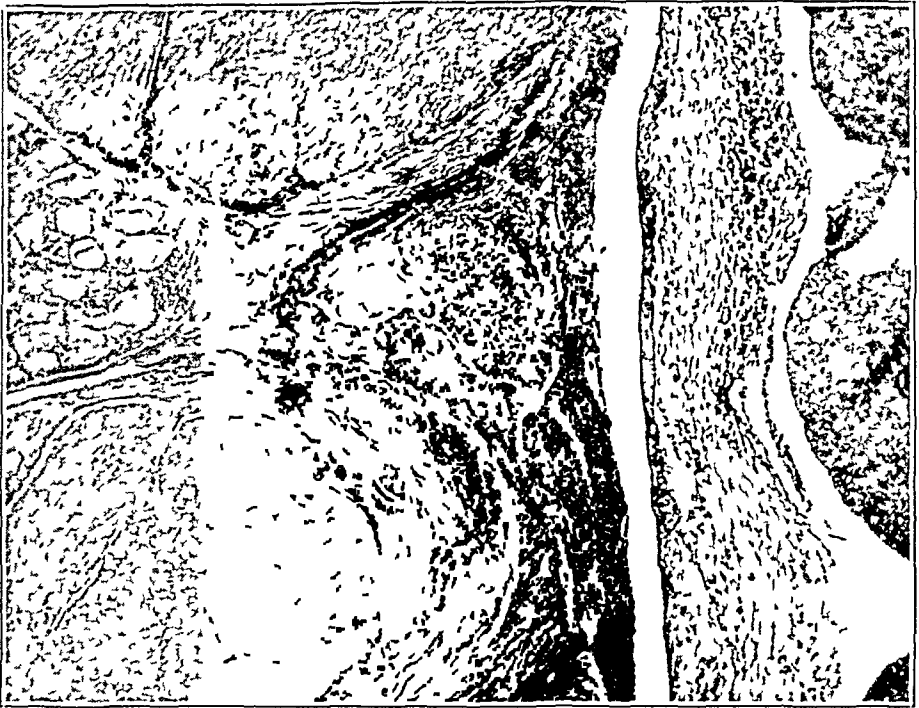


Fig 8—Edema, hemorrhage and cellular infiltration of the dura and nerve roots of the cauda of the monkey referred to in the legend to figure 7 Hematoxylin and eosin stain, $\times 50$



Fig 9—Edema and cellular infiltration of the nerve root and nerve sheaths in the lumbar region of the monkey referred to in the legends to figures 7 and 8 Hematoxylin and eosin stain, $\times 150$

Lesions caused by streptococci isolated from muscles, fascia and the urinary bladder are seen in figure 10. Especially marked were lesions surrounding nerves in the deep muscles of the lower region of the spinal column, in the psoas, in the muscles of the hip, upper parts of the thigh, thorax, posterior aspect of the lower end of the tibia and dorsa of wrists and ankles. The lesions consisted usually of relatively large areas of hemorrhagic infiltration occurring along fascial layers (fig 10 *A* and *B*) and whitish necrotic areas in and between the muscle fibers. These were often numerous in one or in several muscles but were never widely disseminated among many muscles, as were those observed after similar injections of the streptococci of myasthenia gravis.¹ The microscopic

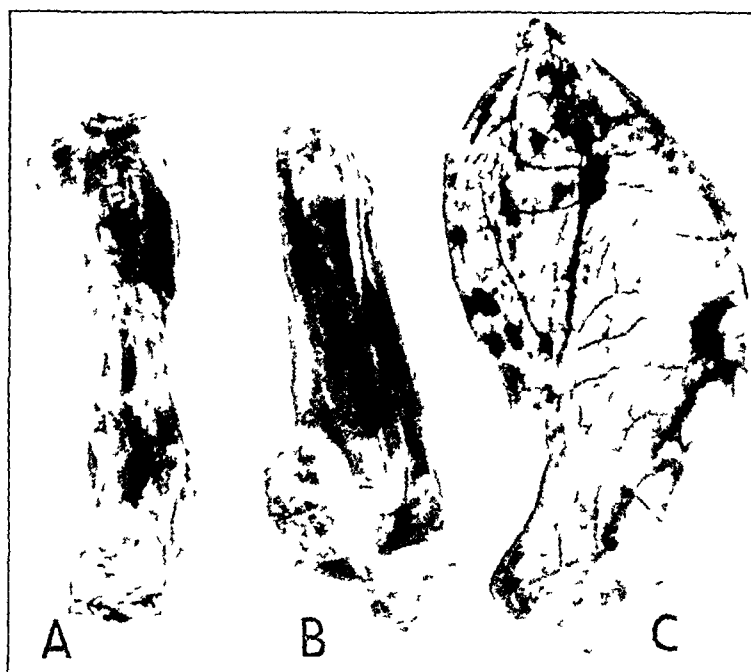


Fig 10—*A* and *B*, edema and hemorrhagic infiltration of the dorsum of the ankle joint and the anterior and lateral aspects of the tibia. *C*, hemorrhages in the urinary bladder of a rabbit inoculated intravenously with streptococci isolated from the stool. $\times \frac{1}{2}$

lesions of the muscles consisted of edema and cellular infiltration of the interstitial tissue and of necrosis, degeneration and cellular infiltration of the muscle fibers (fig 11). Lesions of the ovaries of animals given injections at the time of the epidemic of 1934 were not observed but such lesions were found in 50 per cent of 35 female animals given injections during the present study. They occurred alike in rabbits and monkeys after injection of strains obtained from nasopharyngeal mucus, blood, spinal fluid, muscle and ovary and consisted of severe congestion

¹³ Rosenow, E. C. and Heilman, F. R. Bacteriologic Studies in Myasthenia Gravis, *Proc Soc Exper Biol & Med* **34**: 419-425 (May) 1936.

localized hemorrhages, edema, cellular infiltration and the presence of diplococci in tissue and cystic fluid (fig 12). In almost all pregnant rabbits and mice after injection of the streptococci isolated in the present study abortion occurred.

Lesions of the lungs, of the mucous membrane of the trachea and of the gastrointestinal and urinary tracts (figs 10 *C* and 13) were found in a relatively small number of animals given injections during the epidemic and somewhat later in the present study. Streptococci were isolated from excised pieces of muscle exhibiting lesions in 85 per cent of 33 animals (fig 14 *A*) in the present study, from the brain (fig 14 *B*) in 51 per cent and from the blood in 16 per cent of 60 animals



Fig 11—Edema, degeneration and cellular infiltration of the muscles of 2 rabbits (*A*) five days and (*B*) two days after intravenous injection of streptococci isolated from the spinal fluid. Hematoxylin and eosin stain, $\times 150$.

given injections during the epidemic of 1934, from ovaries showing hemorrhage in 62 per cent of 16 female animals given injections during the present study (table 4, fig 14 *C*) and from the brain in 46 per cent (fig 14 *D*) and from the blood in 30 per cent of 77 animals inoculated during the present study. Control cultures from uninvolved tissues and blood of well animals never yielded streptococci.

In contrast, streptococci were not isolated from the muscles of any of 11 or from the ovaries of any of 9 animals given injections respectively of streptococci from well persons or of filtrates, sterile dextrose-

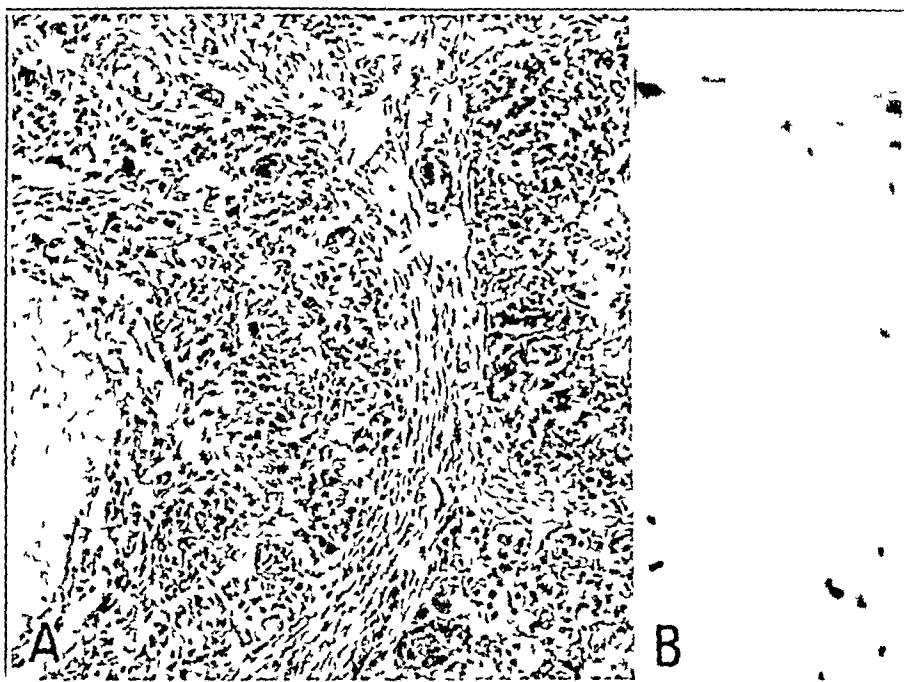


Fig 12—*A*, hemorrhage, necrosis and cellular infiltration in tissues and cellular infiltration in cystic fluid *B*, diplococci in the ovary of a rabbit inoculated intravenously with streptococci isolated from the ovary referred to in the legend for figure 4 (*A*, hematoxylin and eosin stain, $\times 85$, *B*, Rosenow-Gram stain, $\times 1,000$)

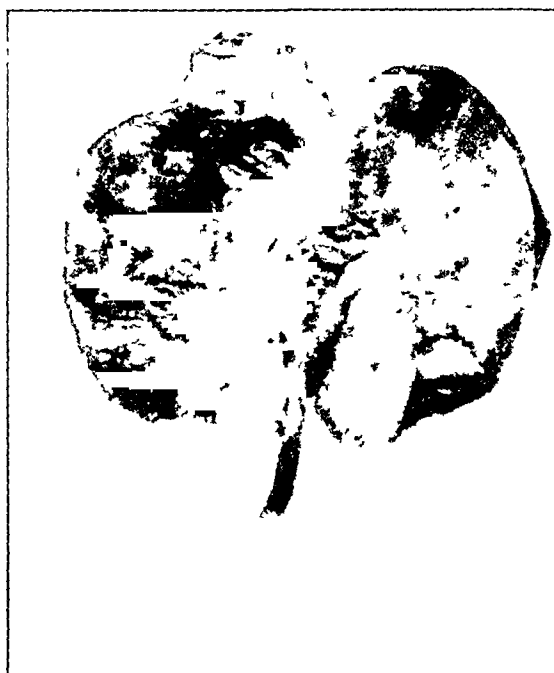


Fig 13—Subcapsular hemorrhage, infarction of the kidney and hemorrhagic infiltration of the ureter of a monkey inoculated intraspinally and intracerebrally with a suspension in gelatin-Locke solution of the nasopharyngeal swabbings from 8 patients $\times 1$

brain broth or saline solution. This striking difference in results in test animals and controls is in accord with results obtained in many other similar experiments. Filtrates of nasopharyngeal washings of patients with this bizarre type of disease were injected intracerebrally by standard methods for the detection of poliomyelitis and encephalitis viruses into rabbits, monkeys and mice. Virus "takes" were not obtained in a single instance.

During the present study 46 mice were given intracerebral or intraperitoneal injections of streptococci obtained from 27 patients. In some tremors and spasms associated with weakness (especially of the hind extremities) followed. Streptococci were isolated from the blood, pleural fluid or brain of 31 of the 42 mice that died.

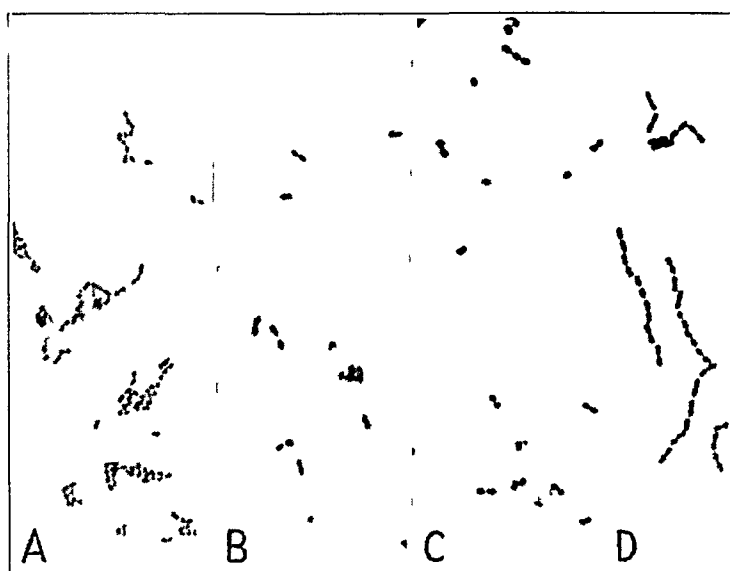


Fig 14—Streptococci isolated in dextrose-brain broth from (A) involved muscle of a monkey and (B) the brain of a monkey at the time of the epidemic of 1934 and (C) the ovary of a rabbit and (D) the brain of a monkey at the time of the present study, after intracerebral or intravenous injection. Gram stain, $\times 1,000$.

The streptococci isolated from characteristic lesions produced by them in animals were grown in pure culture in dextrose-brain broth, and the cultures were filed away in hermetically sealed bottles. These cultures were kept at room temperature without transfer for about eighteen months. Subcultures yielded pure growths of the streptococci in many instances. The first subculture of each of four strains, from the blood, spinal fluid, muscle and ovary, respectively, was injected into rabbits in a manner similar to that used when the strain was first isolated. The animals showed lesions in the muscles, fasciae, dura, nerve roots, ovaries, stomach and urinary tract which resembled in type, distribution

and incidence those produced with the freshly isolated strains. An equal number of control animals given injections of streptococci freshly isolated from patients with colds and encephalitis exhibited no such lesions.

SPECIFIC LOCALIZATION OF STREPTOCOCCI FED TO ANIMALS

In order to determine the specific invasive power of the isolated streptococci with respect to the mucous membrane of the gastrointestinal tract, 12 mice and 12 rabbits were fed material containing the streptococci. As controls, 12 mice and 12 rabbits were given water sterilized with tincture of iodine (1:30,000). The suspensions of streptococci were prepared in such a manner as to contain approximately 2,000,000,000 organisms per cubic centimeter. The experiment was continued for one week, at the end of which all animals that had survived were etherized for examination. Three of the rabbits that received the suspensions died, but none of the mice that received the streptococci and none of the 24 controls died. Lesions were found in 9 of the 12 rabbits that were fed streptococci. They occurred chiefly in the dura mater, in and surrounding nerve roots (radiculitis), in muscles of the thighs, thorax and hips and in the peritoneum, uterus and ovaries. No lesions were observed in the 12 control rabbits. The streptococci were isolated from the brains of 3 of the 12 test rabbits, from the blood of 1, from the muscles of 7, from the peritoneal fluid of 9, from the kidneys of 5 and from the uterus and fetuses of 2 and the ovaries of 3 of the 5 females. In contrast, streptococci were isolated from only 1 of the 12 control rabbits and in that animal only from the liver. Of the 12 test mice which had received living streptococci, the organism was isolated from the livers of 4, from the spleens of 8, and from the ovaries of 5 of the 6 females in the group. In contrast, streptococci were isolated from the livers of only 2 and from the spleen of only 1 of the 12 controls. In no instance were streptococci isolated from the ovaries of the 4 females in this group.

PREPARATION AND USE OF STREPTOCOCCIC VACCINE

As soon as it was found that the streptococci isolated would produce lesions in animals similar to those observed in the patients from whom the organisms had been isolated, a composite vaccine was prepared from strains isolated from nasopharyngeal mucus, blood, spinal fluid and excised muscle. The organisms obtained in representative cases were grown for twenty-four hours in dextrose-brain broth, and the centrifuged bacteria were suspended densely in glycerin (2 parts) and 25 per cent solution of sodium chloride (1 part). This dense suspension was diluted in a solution of sodium chloride equivalent to the density of the

original culture (2,000,000,000 organisms per cubic centimeter) It was then heated to 75 C (167 F) for one hour Sterility tests were made, and phenol to 0.2 per cent was added as a preservative Extreme hypersensitivity to these organisms had been anticipated and was found to be present in most cases Hence, the vaccine was diluted, tenfold, one hundredfold and one thousandfold, respectively, for use In a few patients, who were only moderately sensitive, improvement, sometimes spectacular, followed the subcutaneous injection, at first twice and then once weekly, of gradually increasing doses of the vaccine Most of those who were excessively sensitive either did not improve or were made worse by the vaccine

COMMENT AND CONCLUSIONS

By means of special methods my associates and I have isolated the same type of streptococcus from the nasopharynx, stools and uterine cervix and, during exacerbations of the disease, consistently from catheterized urine, blood, spinal fluid, excised muscles and ovaries of patients suffering from recurring encephalomeningoradiculitis and fibromyositis The common occurrence of infiltration of the dura, especially in the lumbar region, and the almost complete absence of cells in the spinal fluid, of animals given injections of the isolated streptococci indicate that the streptococci isolated from the spinal fluid were really from the infiltrated dura

The almost simultaneous occurrence of exacerbations in many cases, the common presence of gastrointestinal symptoms in patients, the specific localization in animals after injection and feeding and the presence of the streptococci in large numbers in the stool during exacerbations of the disease indicate that the most probable source of infection in these cases was the gastrointestinal tract Infection in teeth and tonsils seemed not to be the source in most of the cases

The chief symptoms and lesions found in patients at the time of our study were reproduced in monkeys, rabbits and mice by intracerebral and intravenous injection and by feeding of the streptococci at the time of isolation and also eighteen months later The findings referable to the ovaries recall the case of acute primary streptococcic ovaritis reported by Wilder¹⁴ The experimental production of ovaritis in animals by injecting streptococci isolated from ovarian tissues recalls the production of ovaritis electively by means of the streptococci isolated from ovaries undergoing sclerosis and cystic degeneration¹⁵ The lesions in nerve roots, fascia and muscles recall the results of similar studies of

14 Wilder, R. M. Peritonitis Following Acute Ovaritis of Anginal Origin, *J. A. M. A.* 66:569-571 (Feb. 19) 1916

15 Rosenow and Davis, cited in footnote 10

epidemic neuromyeloencephalitis,¹⁶ neuromyositis or fibrositis,¹⁷ myositis¹⁸ and myasthenia gravis¹⁹

On the basis of this experience I interpret the deep-seated pains in the back, hips and thighs and the weakness and undue fatigability so common to these patients as due chiefly to infection and intoxication of muscles (myositis), connective tissue (fibrositis), nerve roots (radiculitis) and dura mater (pachymeningitis). I interpret the extreme headache common to these patients as a toxic manifestation rather than as an indication of infection of the brain by the streptococci and infiltration of the dura mater due to the presence of the streptococci, and the extreme pain occurring during menstruation as referable to sclerosing infection of the ovaries.

The filtrable virus, as was to be expected, could not be demonstrated in nasopharyngeal washings and other suspected material, since enduring immunity to and disappearance of the virus occur regularly after frank and after abortive attacks of poliomyelitis in both human beings and monkeys. Immunity acquired during chronic streptococcic infections is of short duration, this seems to explain the recurring exacerbations and remissions which were such striking features of this group of cases. The widespread distribution and the character of the lesions and the extreme sensitiveness to the isolated streptococci and to the vaccine prepared from them may account for the fact that cure of the patients has been difficult.

The conclusion seems warranted, then, that this strange disease actually was not poliomyelitis at the time of our study but was, rather, encephalomeningoradiculitis of the type which is usually associated with fibromyositis, that it was caused by a type of streptococcus having simultaneous affinity in varying degrees for the nervous system, connective tissue, muscles and ovaries and, furthermore, that this type of streptococcus was related to that isolated by us during the epidemic of 1934.

Dr. Hugh T. Jones, of Los Angeles, suggested this study and assisted in the work. Drs. O. J. Sloan and E. T. Remmen, at the Physicians and Surgeons Hospital, Glendale, Calif., provided laboratory space and permitted clinical observations.

16 Rosenow, E. C. Neuromyelo-Encephalitis During and Following an Epidemic of Hiccup. Diverse Localization of Streptococci, *Arch. Neurol. & Psychiat.* **16** 21-36 (July) 1926.

17 Rosenow and Jensen, cited in footnote 10.

18 Rosenow and Ashby, cited in footnote 10.

19 Rosenow, E. C., and Heilman, F. R. Serologic Studies with Streptococci Isolated in Cases of Myasthenia Gravis, *Proc. Soc. Exper. Biol. & Med.* **34** 477-480 (May) 1936, footnote 13.

TUMORS OF THE ADRENAL GLANDS

I A MODIFIED AIR INJECTION ROENTGEN TECHNIC FOR DEMONSTRATING CORTICAL AND MEDULLARY TUMORS

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AND

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The most important element in the diagnosis of an endocrine disease is the demonstration of an anatomically abnormal gland. Recognition of disorders of the thyroid, for example, has been facilitated by the ease with which the gland can be palpated in the neck or visualized by the roentgen rays if it is in the mediastinum. The presence of a tumor of the adrenal gland may not be demonstrable by palpation, displacement of the kidney or roentgen visualization unless the growth is of considerable size. Any method offering greater precision in the recognition of an adrenal tumor early in its history warrants further study. Periadrenal insufflation of air at present yields the most promising diagnostic possibilities. Its technic forms the basis of this study.

There are three clinical syndromes associated with hyperfunctioning tumors of the adrenal cortex, namely, virilism, basophilism and (in the male) feminization. Recognition of these syndromes is easy when the disease is advanced or pronounced but difficult when it is early or mild. Confusion in the diagnosis is possible, since the signs of one syndrome may blend into those of another and since each syndrome may be simulated by disease originating in another gland. There is no infallible clinical or laboratory finding which points to the adrenal cortex as the primary source of the disease. For example, recent assays of the urine of the patient for androgen and estrogen are of limited diagnostic use, since the findings are not characteristic in cases in which the diagnosis is questionable and are definite only in cases in which it is clinically obvious. Demonstration of enlargement of the adrenal gland remains

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This study has been made possible by a surgical assignment to one of us (O. C.), through the cooperation of Drs. E. D. Churchill, A. W. Allen and J. V. Meigs of the Surgical Staff of this hospital.

the most reliable diagnostic measure in a case of suspected adrenal disease

It may be difficult on a clinical basis to distinguish hyperadrenism due to a pheochromocytoma from other types of hypertension. With the progression of hyperadrenism permanent hypertension may develop, resembling other forms of essential hypertension, and the diagnosis is not made unless the patient is observed in a hypertensive crisis. A simple and safe method of visualizing retroperitoneal masses should prove useful in substantiating a clinical impression.

Of the methods commonly available for demonstration of enlargement of the adrenal gland, direct palpation of a tumor in the region of the gland has been the most reliable. The position of the adrenal gland under the dome of the diaphragm, in front of the tenth and eleventh ribs, makes direct palpation of the gland impossible unless it is considerably enlarged. Even at operation through the abdominal cavity, direct palpation of the gland may be misleading. Displacement of a kidney is only suggestive and does not occur to a degree detectable on physical examination unless the tumor is large. Pain from enlargement of the adrenal gland does not occur until either the tumor is massive or malignant extension has taken place. The normal adrenal gland cannot be identified by the ordinary flat roentgenogram. Unless a tumor of the gland has attained a certain size, simple roentgen visualization is not possible, and, as on physical examination, displacement or rotation of the kidney by a tumor above cannot be counted on unless the tumor has reached a diameter of at least 5 cm.

After the introduction of the roentgen rays, use was made of gases as contrast mediums in the peritoneal cavity.¹ Rosenstein^{2a} and Carelli and Sordelli^{3a} reported independently and almost simultaneously in 1921 improved visualization of the kidney by the retroperitoneal injec-

1 Rosenstein and others gave Rautenberg (Rautenberg, E. *Roentgenphotographie der Leber, der Milz und des Zwerchfells*, Deutsche med. Wchnschr. **40** 1205, 1914) credit for the first pneumoperitoneum, although it had been used earlier (Lorey. *Ueber eine Methode die Organe der Bauchhöhle im Röntgenbilde darzustellen*, München med. Wchnschr. **61** 274, 1914).

2 Rosenstein, P. (a) Die "Pneumoradiographie des Nierenlagers," ein neues Verfahren zur radiographischen Darstellung der Nieren und ihrer Nachbarorgane (Nebenniere, Milz, Leber), *Ztschr. f. Urol.* **15** 447, 1921, (b) Erfahrungen mit der Pneumoradiographie des Nierenlagers, *Med. Klin.* **18** 529, 1922.

3 (a) Carelli, H. H., and Sordelli, E. Un nuevo procedimiento para explorar el riñón, *Rev. Asoc. med. argent.* **34** 424, 1921. (b) Carelli, H. H. Sur le pneumopéritoine et sur une méthode personnelle pour voir le rein sans pneumopéritoine, *Bull. et mém. Soc. méd. d'hôp. de Paris* **45** 1409, 1921, (c) El enfisema peri-renal en el diagnóstico radiológico de las afecciones del riñón, *Rev. Asoc. med. argent.* **36** 1127, 1923.

tion of oxygen or carbon dioxide. In both articles delineation of neighboring organs, including the adrenal glands, was described, but neither author suggested use of the method for demonstration of disease of any organ other than the kidney. Workers in different countries were prompt to explore the usefulness of the technic in cases of suspected renal disease. Following Rosenstein's lead, work was reported from Germany,⁴ Finland⁵ and Hungary.⁶ Immediately after his initial report Carelli demonstrated his technic in France,^{3b} Germany, England and the United States. Carelli's example stimulated interest, and minor modifications were suggested.⁷

Complications soon were encountered, mediastinal emphysema and air embolism were recorded. Although deaths from pneumoperitoneum had been reported,⁸ no actual deaths from retroperitoneal perirenal insufflation of air were mentioned until recently.⁹

The first to point out the usefulness of perirenal retroperitoneal insufflation of air in the diagnosis of enlargement of the adrenal glands were Mosenthal^{4b} and Loser and Israel.^{1c} These three authors demonstrated roentgen hyperplasia of the adrenal glands after injection of gas in 2 sisters with virilism. The glands were not, however, proved diseased by operation or autopsy. The report of these cases was apparently lost sight of, and it was not until 1935, when Cahill¹⁰ emphasized

4 (a) Boeminghaus, H. Zur Pneumoradiographie des Nierenlagers, *Ztschr f urol Chir* **9** 51, 1922. (b) Mosenthal, A. Unsere Erfahrungen mit der "Pneumoradiographie des Nierenlagers" nach P. Rosenstein, *ibid* **12** 303, 1923. (c) Loser, A., and Israel, W. Zur Pathologie und Diagnose des Pseudohermaphroditismus femininus externus als innerer Sekretionsstörung, *ibid* **13** 75, 1923.

5 Jansson, C. G. Beitrag zur Pneumoradiographie der Nieren, *Acta chir Scandinav* **58** 311, 1924.

6 Szabo, I. Beitrage zur Pneumoradiographie, *Beitr z klin Chir* **129** 677, 1923.

7 Chevassu and Maingot. A propos de l'insufflation péritoneale, *J d'urol* **13** 54, 1922. L'inconstance des resultats fournis par l'insufflation perirenale, *ibid* **13** 118, 1922. Hernaman-Johnson, F. The Carelli Method of Perirenal Inflation, *Brit M J* **1** 91, 1922. Delherm and Laquerriere. La radiographie du rein par la methode Carelli-Sordelli. Le pneumo-rein, *Presse méd* **30** 133, 1922. Delherm, Laquerriere and Morel-Kahn. Sur un nouveau procede d'exploration radiologique du rein. Le pneumo-peri-nephros, *J de radiol et d'electrol* **6** 369, 1922. Qumby, W. C. Perirenal Insufflation of Oxygen, *J Urol* **9** 13, 1923.

8 Case, J. T. A Review of Three Years' Work and Articles on Pneumoperitoneum, *Am J Roentgenol* **8** 714, 1921.

9 Fish, G. W., (a) in discussion on Roome, N. W. Visualization of the Adrenal Glands by Air Injection, *J A M A* **112** 196 (Jan 21) 1939, (b) personal communication to the authors.

10 Cahill, G. F. Air Injections to Demonstrate the Adrenals by X-Ray, *J Urol* **34** 238, 1935. Cahill, G. F., Loeb, R. F., Kurzrok, R., Stout, A. P., and Smith, F. M. Adrenal Cortical Tumors, *Surg, Gynec & Obst* **62** 287, 1936. Cahill, G. F. The Adrenogenital Syndrome and Adrenocortical Tumors, *New England J Med* **218** 803, 1938.

the advantages of retroperitoneal injection of air in disclosing tumors of the adrenal glands, that the procedure finally received the recognition it deserves¹¹ Between the dates of publication of the paper by Loser and Israel and that by Cahill, seven papers appeared describing the use of retroperitoneal injection of gas¹² In all of these papers only diseases of the kidney itself were considered, and with the development of improved pyelographic methods, the gas injection procedure fell into disuse

Since the publication of Cahill's papers, Mencher,¹³ Gianturco and Dienckhahn¹⁴ and Roome¹⁵ have added their recommendations of the procedure in the diagnosis of disease of the adrenal glands In spite of these reports, Walters and Kepler¹⁶ stated that they are unimpressed by the possibilities of the technic In view of the possible hazards of the procedure, their skepticism is not without justification Since all untoward effects are avoidable by use of the modified technic to be described in this paper, reconsideration of the procedure is necessary at this time in order that a useful technic shall not fall into disrepute

The present study is based on 163 separate injections of air in 78 patients In all of the cases studied there was some clinical reason to suspect disease of the adrenal glands The size of the shadows outlined by air, visualized on the roentgen film, was confirmed by operative

11 Langeron and his associates demonstrated a large suprarenal tumor by intraperitoneal insufflation of air (Langeron, L., Decherf, E., and Danes. *Epithélioma cortico-surrénal avec virilisme et hirsutisme. Localisation par le pneumo-péritoine, extirpation chirurgicale*, Bull et mém Soc méd d hop de Paris **53** 436, 1929) Because of the intervening peritoneum and renal fascia, air in the peritoneal cavity will not outline a normal adrenal gland or a small tumor of the gland

12 Roseno, A., and Hartoch, H. *Das Pneumoradiogramm des Nierenlagers bei der Gallenblasendarstellung. Ein neuer Weg zu verfeinerter Diagnostik*, Deutsche Ztschr f Chir **198** 250, 1926 Schilling, H. *Pneumo-Radiography of the Kidney*, Internat Clin **4** 138, 1927 Gottlieb, J. *Ueber Pneumoren*, Ztschr f Urol **21** 32, 1927 Dozsa, E. *Ueber die Indikation, diagnostische Bewertung und Gefahren der Pneumoradiographie*, Ztschr f urol Chir **28** 365, 1929 Schuller, J. *Zur Frage des Skrotalemphysems nach Nierenoperationen*, Ztschr f Urol **24** 345, 1930 Viethen, H. *Technik und Indikationsstellung der Pneumoradiographie des Nierenlagers*, *ibid* **25** 1, 1931 Jansson⁵

13 Mencher, W. H. *Perirenal Insufflation*, J A M A **109** 1338 (Oct 23) 1937

14 Gianturco, C., and Dienckhahn, C. H. *The Role of Perirenal Injections of Gas in the Radiological Study of the Adrenal Glands*, Radiology **30** 500, 1938

15 Roome, N. W. *Visualization of the Adrenal Glands by Air Injection*, J A M A **112**:196 (Jan 21) 1939

16 Walters, W., and Kepler, E. J. *Adrenal Cortical Tumors and Their Treatment. A Study of Seven Operated Cases*, Ann Surg **107** 881, 1938

exposure through a retroperitoneal approach¹⁷ in 15 patients and by postmortem examination of 2 patients

TECHNIC

Site of Injection—The success of the air injection technic for visualization of the adirenal glands depends on the anatomic fact that the renal fascia, or fascia of Gerota, forms a compartment which encloses both the adrenal gland and the kidney. Air injected anywhere in this compartment diffuses throughout the perinephric fat, outlining the two organs into which the air does not penetrate.

The site of choice for injection of air into the perirenal space is the triangular fat pad below the kidney. The kidney is suspended partly by its vascular attachment, partly by fine bands of connective tissue running through the perinephric fat from the renal capsule to the renal fascia and partly by the pressure of the surrounding organs. The lower pole of the kidney rests in a mass of fat which lies between the anterior and posterior folds of renal fascia above the pelvic brim.

The presence of a ptotic kidney is first excluded by palpation or by roentgen examination. One per cent aqueous solution of procaine hydrochloride is injected into the skin with a fine needle just above the iliac crest, lateral to the semispinalis muscle (fig. 1). Two cubic centimeters of the procaine solution is then injected into the subcutaneous fat and external fascia, medial to the expected line of insertion of the needle. A 20 gage lumbar puncture needle with a stilet is passed through in the following order: the skin, the subcutaneous fat, the fused posterior and medial layers of the lumbodorsal fascia, the quadratus lumborum muscle in its lower and lateral portion, the anterior layer of the lumbodorsal fascia, the thin layer of paranephric fat and, finally, the posterior fold of the renal fascia, into the perinephric fat. After passing through the renal fascia the needle slips readily through the fat for 2 to 3 cm until the anterior fold of the fascia is reached. Pushing the needle back and forth for 1 to 2 cm in this space without encountering obstructing fascia is virtual anatomic proof of the position of the point.

With care and practice the needle can be felt to pass through each of these layers. As it is inserted the needle point passes not only anteriorly but slightly medially. In the route described the needle avoids the semispinalis and psoas muscles. If it is inserted too far medially it will penetrate the psoas muscle, and the distance traversed will have to be much greater before the perinephric space is reached. Also, the posterior leaf of the renal fascia thins out medially, and a less distinct

¹⁷ Cope, O. Tumors of the Suprarenal Glands. III. Description of a Retroperitoneal Subdiaphragmatic Operative Approach to the Suprarenal Gland, to be published.

click is felt when the needle passes through it. Injection of the air behind the renal fascia, as in the peritoneal cavity, although it may outline a large tumor and the diaphragm, will not delineate the normal adrenal gland or a small mass.

When the needle is believed to be in place the stilet is withdrawn, a syringe containing the procaine is fitted and the plunger is withdrawn



Fig 1—*A*, patient in position for injection on either side. A thin pillow is placed under the lower part of the chest and if necessary under the pelvis to obviate lumbar lordosis. The twelfth rib, the spinous processes, the crest of the ilium and the lateral border of the semispinalis muscle are marked. The circle indicates the optimal site of injection. The cross shows the usual but incorrect point of injection. *B*, closer view, taken from above the head of the patient, showing the angle of insertion of the needle in a patient of this build.

to make sure that the point is not within an aberrant vessel. Two cubic centimeters of the anesthetic solution is then injected. A second test of the position of the needle point is now possible, if the needle is still

in the muscle the solution enters only under pressure, if it is in fat tissue the solution runs in readily and can also be withdrawn. The syringe is now replaced by a glass adapter. This¹⁸ is attached by rubber tubing to a second glass adapter, packed with sterile cotton, which in turn is connected to a 50 cc tight-fitting ordinary syringe (fig 2). A second withdrawal of the plunger is then advisable, and if the anesthetic solution and no blood returns, the injection of air is started.

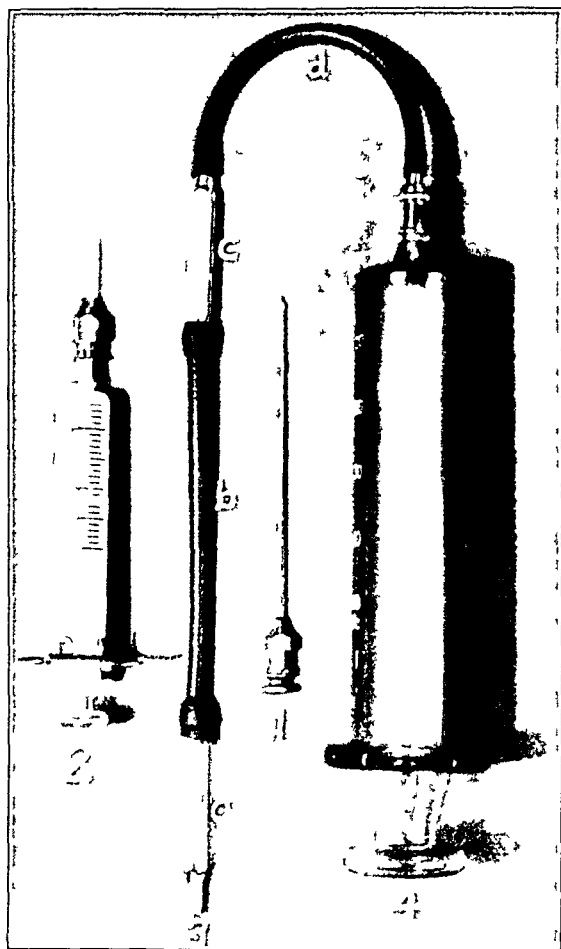


Fig 2—Paraphernalia required for injection of air. 1, 20 gage lumbar puncture needle with stilet, 2, 5 cc syringe with a no. 25 needle, 3, empty glass adapter (*a*), rubber tube (*b*), glass adapter packed with cotton (*c*) and connection rubber tubing (*d*). 4, 50 cc tight-fitting glass syringe. A clip or three way stopcock to close the rubber tubing while the syringe is being refilled with air is not needed, since the air is injected under low pressure. The rubber tubing may be closed between the fingers or left open.

Volume of Injection—Two hundred cubic centimeters of air is ample for the adult, for a child smaller quantities are used. Larger volumes, although recommended by others, are unnecessary, the larger

¹⁸ More complicated apparatus is not necessary. A water manometer connected with the circuit is advisable while learning the procedure.

the volume, the greater the pressure required to complete the injection. Higher pressures increase the risk and the discomfort.

Rate of Injection and Pressure—Not less than ten minutes is required to inject the air. The air as well as the anesthetic solution enters readily if the needle point is in the correct place. The pressure required for the injection of the air need never exceed 25 cm. of water, a pressure of 15 to 18 cm. usually suffices. Withdrawals of the plunger during the injection are wise. If the needle is in the right space, air will be recovered.

COMPLICATIONS

The technic used at this hospital has been particularly designed to avoid the following possible complications:

Air Embolism—The most frequently reported complication of periadrenal injection of air is air embolism. Except for the 2 deaths recorded by Fish,^{9a} the reports in the literature have been of nonfatal embolism. A report, however, has come from another clinic of a recent death from an embolism authenticated by autopsy and by postmortem roentgen examination.^{9b}

In injecting the air one is tempted to insert the needle point as near the gland as possible. In all accounts in the literature, exactly this procedure is recommended. In view of the vascularity of the region and of the adrenal gland itself, it is unwise to pass a needle into this area. Besides the three sets of vessels supplying the adrenal gland, the vessels to the other retroperitoneal organs, the pancreas, duodenum, spleen and kidneys, as well as the vena cava on the right side, must be considered. The aorta, with its pulsation and its thicker wall, is readily recognized and avoided. Penetration of any one of the veins may result not only in a hematoma but, on injection of the air, in embolism. In the anatomically well defined area recommended in this paper as the site of injection, only the minute vessels supplying the perinephric fat itself are present.

Besides the vascularity of the region, the rate of injection should play a role in the prevention of air embolism. If the needle is moved during the injection and the air enters a vein, the danger is minimized if the rate of injection is as slow as has been recommended. The 20 per cent of oxygen in the air is absorbed rapidly by the blood, and such nitrogen as is not absorbed immediately is found as small peripheral emboli in the lungs. To produce an embolus of sufficient size to cause circulatory embarrassment this volume of air would have to be injected much more rapidly.

The use of oxygen instead of air has been considered, since with its use there would be less danger of peripheral emboli in the lungs.

As will be pointed out under "Interpretation," however, many hours are sometimes required for proper diffusion of the gas, and oxygen is so rapidly absorbed from the tissues that good visualization of the adrenal glands would not always be obtained. The even more rapid absorption of carbon dioxide excludes the use of this gas in spite of its rapid rate of diffusion.

No signs or symptoms of an embolism occurred in the patients in this series.

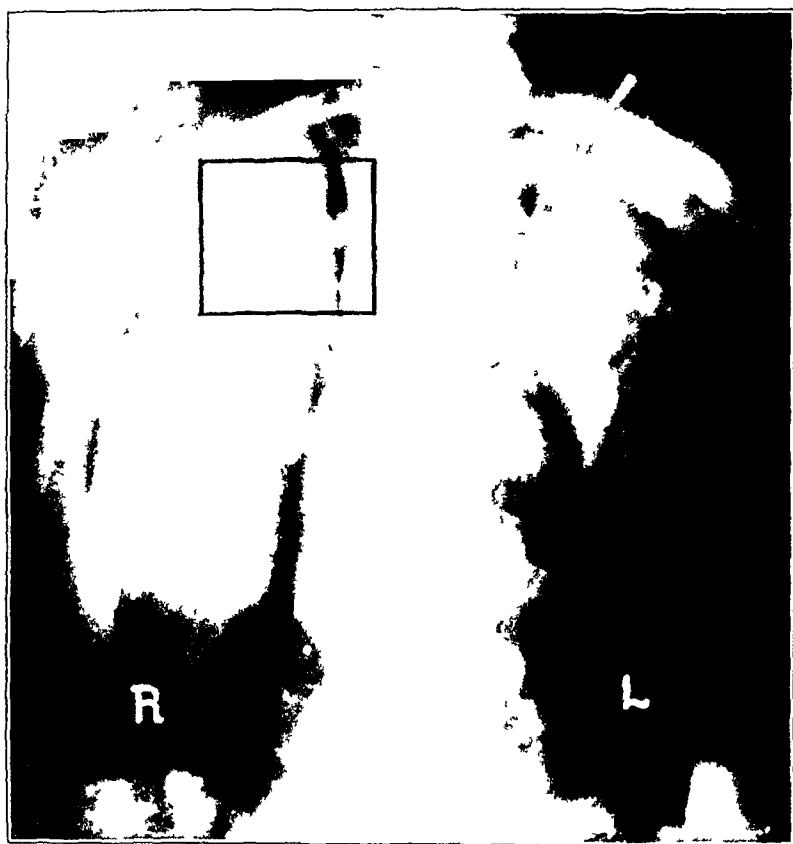


Fig 3 (case 20) —Anteroposterior plate taken one-half hour after simultaneous bilateral periadrenal insufflation. A small mass, larger and denser than a normal adrenal gland, is seen occupying the right suprarenal space (see square). A normal adrenal gland is outlined on the left side (white arrow). The shadows of both kidneys are normal.

Hematoma of the Renal Capsule —When the needle is inserted the kidney must be scrupulously avoided. In the twentieth case of this series the needle was felt to enter the capsule of the kidney. Blood oozed slowly from the needle. The needle was therefore withdrawn and inserted below the kidney, and the air was injected. The roentgenograms taken within one-half hour after the injection showed the outlines of a normal kidney (fig 3). The films taken twenty-four hours later revealed an

enlarged, irregular, indistinct renal shadow (fig 4). The patient, whose case has been reported elsewhere by Palmer and Castleman,¹⁹ died six days later in one of her frequent hypertensive crises. At postmortem examination a large hematoma distending the true renal capsule and compressing but not involving the renal substance was found (fig 5). Although it was undoubtedly not the direct cause of the death of this patient, a similar complication in another patient might well be the contributing or final cause of death. Had the hematoma been on the

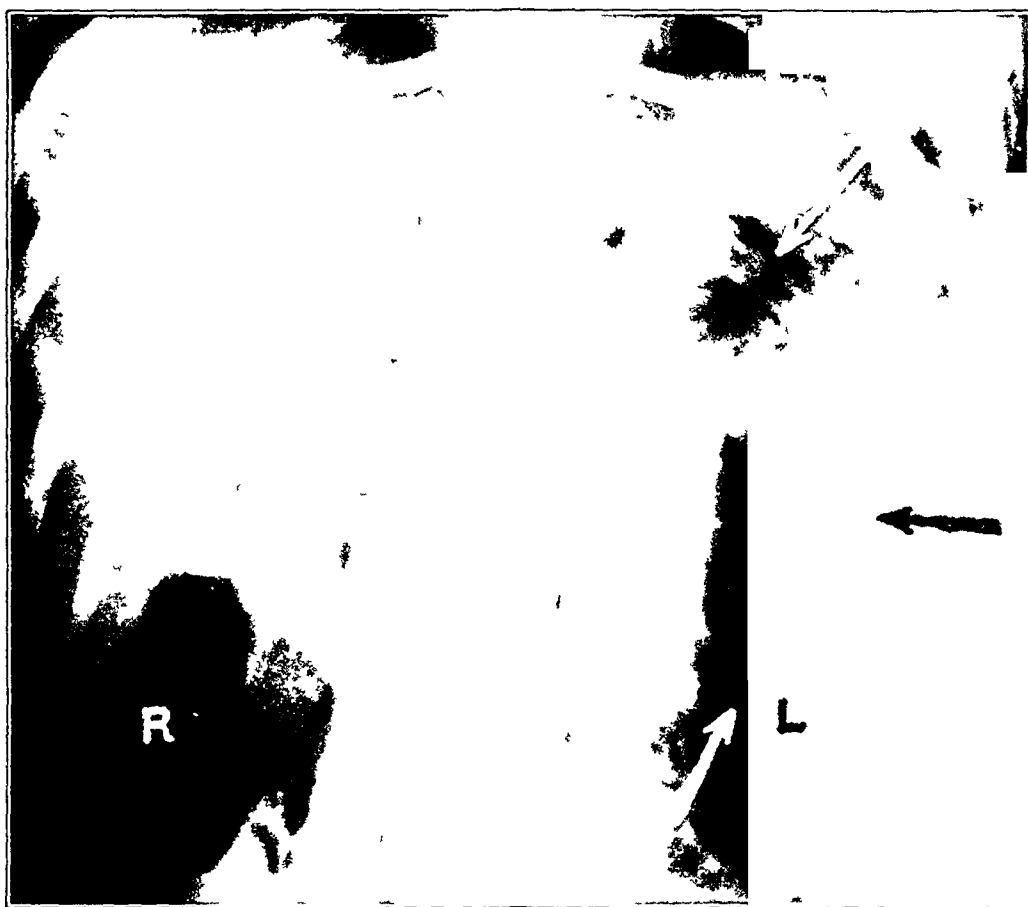


Fig 4 (case 20) —Anteroposterior plate taken twenty-four hours after figure 3. The tumor of the right adrenal gland and the kidney are as previously outlined. The shadow of the left kidney is enlarged and irregular, with indistinct margins (white arrows). The shadow of the normal left adrenal gland is still visible. Compare with figures 3 and 6.

side of the pheochromocytoma a fatal outpouring of adrenin by direct pressure on the tumor might have occurred. The experience gained in this case emphasized the importance of introducing the needle into the perirenal space, well away from the kidney.

19 Palmer, R. S., and Castleman, B. Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension, *New England J Med* 219:793, 1938.

Hematoma of the Adrenal Gland—The fragility of the rich vascular network of the adrenal gland itself must be emphasized. Inconsiderate handling of the gland at operation may result in such rapid formation of a hematoma within the substance of the gland that an apparent tumor exists by the time the gland is completely exposed. We have seen elsewhere two normal glands removed because of such hematoma formation. Because of the delicate capsule and the paucity of supporting stroma a needle may easily be run through the adrenal gland without the operator being aware of it. A hematoma may occur as a result, and after the insufflation of an apparent tumor, in reality the hematoma, may be

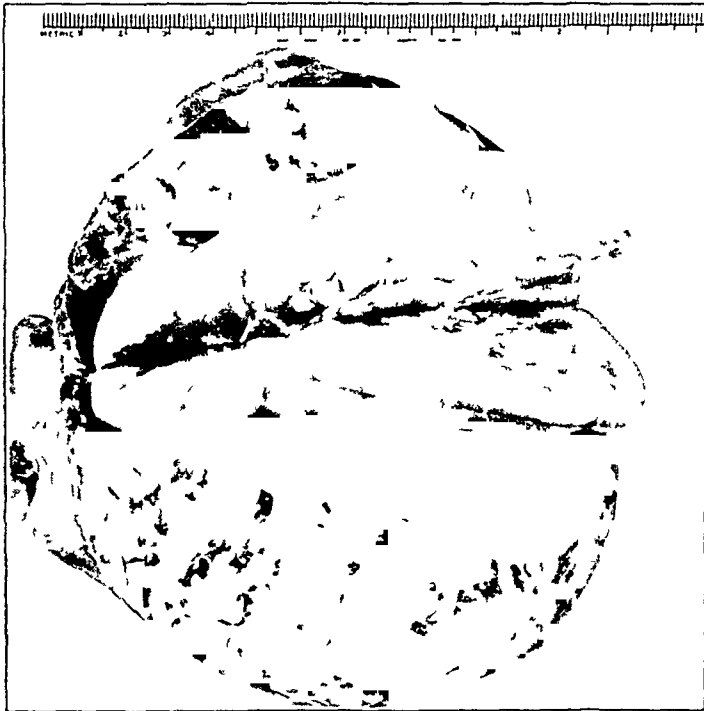


Fig 5 (case 20) —Left kidney compressed by a hematoma within the true renal capsule, found at autopsy six days after a needle puncture wound. No hemorrhage is visible within the substance of the kidney.

outlined. Although this complication has not been met in this series of injections, the possibility of its occurrence is sufficient reason for introducing the needle at the site described.

Expression of Adrenin—In the use of this technic in uncovering medullary tumors another point must be kept strictly in mind. Adrenin is readily expressed from such tumors, and sudden death has been reported from palpation of these tumors with discharge into the circulation of insupportable quantities of the secretion.²⁰ In a young woman

20 Howard, J. E., and Barker, W. H. Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Pheochromocytomata), *Bull. Johns Hopkins Hosp.* 61: 371, 1937.

with a pheochromocytoma in this series, the worst attacks had followed increased abdominal pressure caused by her infant sitting on her abdomen. In injecting air care must be taken to avoid everything but minimum pressure. For this reason, obviously the smallest possible quantity of air should be used.

Pain—Another reason for the low pressure and slow rate of injection of the air is the avoidance of pain. With the slow inflation of the perinephric space, at most a feeling of fulness is noticed deep in the flank or abdomen, comparable to the sensation of a distended stomach. Rapid injection of air may cause sharp pain. Although presumably this pain is produced by overdistention of the connective tissue spaces, actual rupture of the connective tissue must be considered. In 6 of the operative cases, exploration of the suprarenal and perinephric areas was done from three to thirty-eight days after injection of air. In none of the cases were there signs of rupture of any vessels. The 1 case in which there was any blood in the perinephric fat was the case in which a hematoma of the renal capsule was observed at autopsy. The blood presumably had oozed from the puncture wound in the renal capsule.²¹

Injection of air into the muscle layers results not only in an unsuccessful roentgen examination but in pain. In some of the earlier cases the injections were followed by considerable discomfort. In all of them air had infiltrated up through the psoas muscle, in some passing through the diaphragmatic crura into the mediastinum. When the latter occurred, some sensation of suffocation was noticed. In 2 cases air in twenty-four hours reached the neck, where it could readily be palpated. In none of the cases in which air was injected slowly and within the renal fascia was there undue discomfort or did the air pass above the diaphragm.

Fat Embolism—Fat embolism has been suggested as a cause of death following injection of air. Although we are skeptical of the possibility of fat embolism under these circumstances, it cannot be dismissed on the available evidence.

INTERPRETATION

After the injection the patient is asked to walk around for at least half an hour. Massage of the loin, recommended by Cahill, has not been found necessary. Sometimes good delineation of the kidney and adrenal gland is obtained within a half hour. In the majority of cases more complete diffusion of the air and therefore better visualization of the organs is obtained after twenty-four hours. It has been the practice

21 At operation in 2 cases air was still present in the tissues. The presence of the air in no way presented an operative difficulty.

in all cases to take two sets of plates, one within an hour after the injection and the second twenty-four hours later. Anteroposterior and lateral views are taken each time. No special preparation of the gastrointestinal tract is necessary, but the colon should be clean. In order to obtain clearer lateral plates in the last 40 cases, air was injected on one side at a time except under special circumstances. One week is allowed to elapse between injections. In seven days practically all of the air has been absorbed. Dividing the examination into two parts has the added advantage of diminishing the feeling of distention.

The normal adrenal gland is not always visualized on the air injection roentgenograms. When outlined, in its variety of shapes it conforms closely to the gross anatomy of the adrenal gland as seen at operation or autopsy. The left gland is generally elongated, the right, pyramidal. In all cases in which suspected hyperplasia has been demonstrated at operation, a shadow corresponding to the operative finding has been visualized on the roentgenogram. One atrophied adrenal gland exposed at operation had not been visualized on any of the plates, and one normal gland, similarly verified, had been visualized on some but not all of the films.

A shadow representing an adrenal gland is identified on the roentgenogram by the preciseness of form and outline, the relative density and the position above the kidney. In none of the cases in which the diagnosis was verified has such a clearly defined mass not proved to be adrenal tissue. A difficulty in interpretation is caused by superimposed irregular shadows cast by the fat and connective tissue surrounding the gland. The density of the shadow cast by the normal gland is ordinarily greater than that cast by surrounding tissues but is less than that cast by the upper pole of the kidney.

The anteroposterior film gives the most satisfactory results, but lateral plates are advised as controls. Intravenous pyelographic studies have been made simultaneously with the air injection films in many cases. Since the injected air outlines the kidney so well, this procedure has not added anything to the knowledge of the adrenal gland.

USES

We have found periadrenal injection of air useful under the following circumstances:

1. Visualization of a small tumor not demonstrable by other means.

In figure 3 injected air is shown to have outlined a small tumor of the adrenal medulla. The tumor is recognized not only by its size and density, both of which are greater than those of the normal gland on the opposite side, but by the convex lateral and medial borders. The

tumor (fig 6) was not visualized on the films taken for the intravenous pyelogram (fig 7). The case is reported elsewhere¹⁹

2 Exclusion of the adrenal glands as the primary source of disease by demonstration of normal shadows of these glands

The syndromes sometimes associated with enlargement of the adrenal glands may be simulated, both clinically and in the laboratory findings, by disease elsewhere. Exclusion of disease of the adrenal glands by the



Fig 6 (case 20) —Intravenous pyelogram before injection of air. The tumor of the adrenal gland is not identifiable, its mass not being sufficient to cast a separate shadow or to displace or rotate the right kidney.

demonstration of normal shadows helps to direct attention and, therefore, therapy to the proper site.

3 Demonstration of the presence or absence of a normal adrenal gland when a large tumor exists in the contralateral side.

The high mortality reported¹⁶ as immediately following the removal of a tumor of the adrenal gland is due presumably to acute cortical insufficiency. The normal cortical tissue remaining after removal of the tumor is insufficient to supply the requirements of adrenal cortical hormone. The reported incidence of the absence of a normal gland in

the side opposite the tumor is thought to be due to atrophy from disuse of that normal gland. It is essential to demonstrate the existence of normal tissue before excision of a tumor, subtotal excision of the tumor being indicated if adequate normal tissue is not found. Demonstration by injection of air of a normal gland on the side opposite the tumor may preclude an operation, since satisfactory exposure of the adrenal glands is accomplished only through a posterior retroperitoneal approach,¹⁷ necessitating a separate incision for exploration of each gland.

4 Visualization of bilateral hyperplasia of the adrenal glands

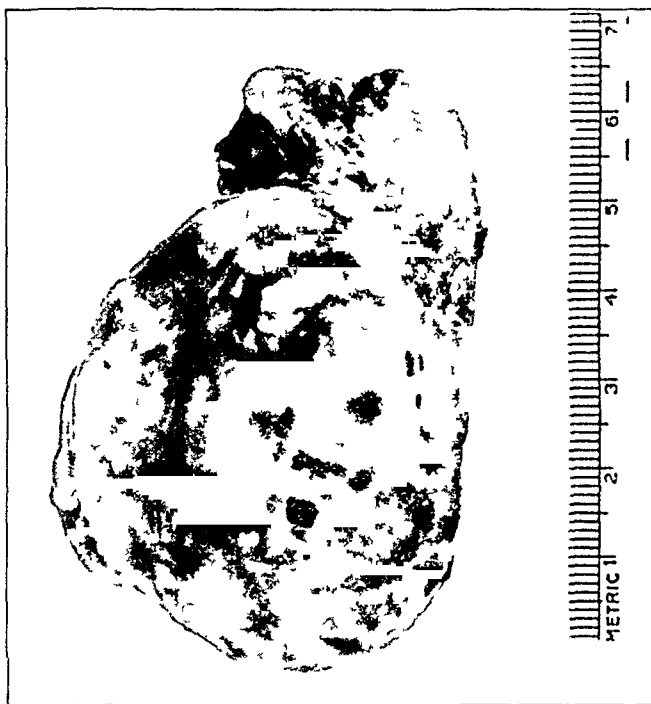


Fig 7 (case 20) —Tumor of the adrenal medulla, removed at autopsy from the right side. The body of the normal right adrenal cortex is shown on the superior and medial surface of the tumor.

The pathologic picture of hyperplasia of the adrenal cortex is not as yet on certain ground. All that can be said at present is that hyperplasia of the cortical layers may exist as a primary source of disease and that grossly the adrenal glands are enlarged in all diameters. The shadows cast by these enlarged glands with the air insufflation technic, although larger than those of the average normal gland, may be so nearly within normal limits that by the roentgen picture alone it may not be possible to make a diagnosis of cortical hyperplasia. In this field of adrenal cortical disease, therefore, the air injection technic is limited in its usefulness.

5 Differentiation of shadows mistaken for those of tumors of the adrenal glands

Two patients have been referred to us in whose cases endocrine disease was suspected and flat roentgenograms had shown a shadow suggestive of tumor of the adrenal gland. In each case the error in interpretation was made apparent by the air insufflation technic.

COMMENT

Any procedure requiring insertion of a needle and injection of air is accompanied by some hazard. With the safeguards outlined, however, the procedure of periadrenal insufflation of air is a simple one which can be performed on an ambulatory patient. In the 163 separate injections there have been no fatalities and no signs of air embolism. The only complications occurred in the first 20 cases, in which the site of injection recommended in the literature was used. Besides the patient who had a hematoma of the kidney, there were 4 who had considerable discomfort. In each of these 4 air had escaped into the mediastinum owing to improper location of the needle outside the renal fascia.

In many of the articles in the literature advising modifications of the technic, statements are made that the needle should be passed so many centimeters in such and such a direction. The variation in anatomy of the individual patient is so great that such instructions are only misleading. To carry out the procedure properly surgical judgment is needed. Knowledge of the anatomy, although requisite, is not sufficient. Impetuosity, lack of precision and failure to check carefully the position of the needle will lead to complications and lack of success.

In spite of the safeguards the procedure is not recommended without reservation. It should be used only for patients in whose cases there is definite suspicion of disease of the adrenal glands. Its major use will be found in including or excluding the adrenal gland as the source of disease. It has been pointed out also that operative exploration of the uninvolved adrenal gland may be obviated by its use in the case of a patient known to have a tumor. Since the risk of periadrenal insufflation of air is less than that of direct operative exploration of a gland, the operative mortality rate for patients with disease of the adrenal glands should be lowered.

Except for the single cases reported by Mencher and Roome, the use of the technic reported in the literature has been limited to disorders of the adrenal cortex. Little attention has been paid to its applicability to adrenal medullary disease. There are two reasons, however, which make it more difficult to disclose a pheochromocytoma than a tumor of the cortex. In the first place, pheochromocytomas occur more often in medullary tissue outside the adrenal gland than do cortical tumors in ectopic cortical tissue. The air infiltration must, therefore, cover a

wider field of the retroperitoneal region. In the second place, the average size of the reported adrenin-secreting tumors is smaller. The possible hazard from the expression of adrenin from a pheochromocytoma during the injection of air is to be emphasized.

There will always be a limit to the amount of information which can be deduced from the roentgenograms, no matter how well the technical procedures of the air injection are completed. The absence of a suprarenal shadow, even though the distribution of the air in the perirenal space is adequate, does not necessarily mean that an adrenal gland is absent or atrophied. The presence of a shadow consistent with that cast by a normal gland cannot exclude absolutely the presence of a small tumor or of hyperplasia.

SUMMARY AND CONCLUSIONS

A modified technic for visualization of the adrenal glands by the injection of air into the renal space is described. In order to avoid complications, air is injected slowly, under low pressure, in small volume and into the lower rather than the upper portion of the renal space. The uses and limitations of the procedure as indicated by the results of 163 injections in 78 patients are discussed.

It is concluded that this procedure can be performed on ambulatory patients and without fatality if the proper safeguards are employed. It is an important adjunct in the inclusion or exclusion of disease of the adrenal gland, either cortical or medullary. By its use, not only can tumors be diagnosed earlier in the course of the disease but operative explorations of the adrenal glands can in certain cases be obviated. The mortality in the treatment of patients suspected of having disease of these glands will, therefore, be lower.

ELEVATION OF UREA NITROGEN CONTENT OF THE BLOOD FOLLOWING HEMATEMESIS OR MELENA

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AND

RICHARD J STEVENS, MD

WITH THE TECHNICAL ASSISTANCE OF ELLEN S GARBER, MS
CINCINNATI

In the past few years a number of reports have appeared on the frequency and significance of azotemia following massive hemorrhage from the upper part of the digestive tract. The first of these communications were those of Sanguinetti¹ who in 1933 and 1934 reported elevation of the urea nitrogen content of the blood in 9 cases of gastric or duodenal ulcer with hemorrhage. He assumed that this increase was due chiefly to absorption of products of decomposition of the blood in the intestinal tract, resulting in a state of intoxication which might prove fatal. He actually recommended cecostomy in order to remove this blood. He reported significant elevation of urea in the blood of 2 of 3 persons fed pig's blood.

In 1935, Christiansen² found elevation of the urea content of the blood and absence of urinary chlorides in 2 cases of bleeding gastric ulcer. He concluded that these changes were due to absorption of toxic substances resulting from bacterial decomposition of the blood in the intestinal tract in addition to a diminished supply of chlorides in the diet. One of his patients showed no pathologic changes in the kidneys.

In the same year there appeared the reports of Sučić,³ Ingegno⁴ and Meyler.⁵ Sučić reported elevation of the urea content of the blood

* Justin A. Rollman Fellow in Internal Medicine, 1938-1939

This study was aided by a grant from Parke, Davis & Company, through the cooperation of Dr. E. A. Sharp.

From the Department of Internal Medicine, University of Cincinnati, and the Gastric Laboratory of the Cincinnati General Hospital.

1 Sanguinetti, L. V. Curvas azohemicas en las hemorragias retenidas del tubo digestivo, Arch. argent. de enferm. d. ap. digest. y de la nutrición 9:68-75, 1933, Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo (estudio clínico y experimental), *ibid.* 9:264-287, 1934.

2 Christiansen, T. Uraemia as Cause of Death in Massive Haemorrhage from Peptic Ulcer, Acta med. Scandinav. 85:333-345, 1935.

3 Sučić, D. Akute Azotämie bei grossen gastro-intestinalen Blutungen, Klin. Wchnschr. 14:1316-1318, 1935.

(Footnotes continued on next page)

of 6 of 7 patients, 5 of whom had a duodenal ulcer, 1 a gastric ulcer and 1 cirrhosis of the liver. He fed 500 and 1,000 Gm of calf's blood respectively to 2 patients and noted no increase in the urea content of the blood one and two days later. He reported no increase of this constituent in the blood of 5 patients with hemoptysis, in that of 2 persons subjected to relative starvation for three days or in that of 1 professional donor after venesection and removal of 600 cc of blood. He concluded that the condition should not be ascribed to dehydration, because it can develop in spite of adequate administration of fluids.

Ingegno⁴ found a value for blood urea of 38 mg or more per hundred cubic centimeters in 17 of 42 cases of hemorrhage due to peptic ulcer. He stated that "the high nitrogen figures were found almost exclusively in those examined within three days of the acute episode" and that persistent or increasing elevation of the value for urea pointed to continuation of bleeding. There was no significant correlation between the degree of anemia and the azotemia. Like Sanguinetti, he concluded that the most significant factor in elevation of the urea content of the blood was the protein of the blood liberated in the gastrointestinal tract. He stated that such factors as hemorrhage per se, shock dehydration and starvation might also play a role. He reported normal concentration of blood chlorides in 5 cases and normal carbon dioxide-combining power of the blood in several cases, but gave no figures.

Meyler⁵ noted elevation of the urea nitrogen content of the blood of 4 patients with bleeding peptic ulcer and concluded that the increase was due primarily to increased destruction of body protein associated with dehydration and starvation. He reported elevation of the blood chlorides of 2 patients and a normal concentration in the case of a third. In 1 instance he noted an increase in the indican content of the blood.

In 1936 there appeared Christiansen's⁶ second report, in addition to reports by Alsted,⁷ Clausen⁸ and Borst⁹. Christiansen found eleva-

4 Ingegno, A. P. Elevated Blood Urea of Acute Gastrointestinal Hemorrhage and Its Significance, *Am J M Sc* **190** 770-774, 1935.

5 Meyler, L. Post-Haemorrhagic Uraemia, *Acta med Scandinav* **87** 313-325, 1935.

6 Christiansen, T. Hyperazotaemia in Intraintestinal Haemorrhage, *Acta med Scandinav*, 1936, supp 78, pp 894-899.

7 Alsted, G. Further Studies on Azotemia Following Hemorrhage in the Digestive Tract, *Am J M Sc* **192** 199-208, 1936.

8 Clausen, J. Hyperazotemia in Cases of Acute Ventricle Hemorrhage, *Acta med Scandinav*, 1936, supp 78, pp 908-914.

9 Borst, J. G. G. Ueber Erhöhung des Kochsalz- und Harnstoffgehaltes und Erniedrigung des Albumingehaltes des Blutes bei Patienten mit starken Magenblutungen, *Ztschr f klin Med* **130** 74-96, 1936.

tion of the value for urea in 17 of 19 cases in which hemorrhage occurred and stated that the elevation may occur in cases of bleeding due to carcinoma as well as of bleeding due to peptic ulcer or to ruptured esophageal varix. He found that achloruria was not an essential accompaniment as he had at first thought and that the urea content of the blood decreased with the patient on a liberal diet without supplementary administration of sodium chloride. He concluded that the elevated value for urea does not necessarily indicate an unfavorable prognosis unless it persists, progresses or is complicated by achloruria. Later he¹⁰ stated that the presence of blood in the intestinal tract is a prerequisite for the development of the azotemia, as no rise in the concentration of urea in the blood occurred when the blood was lost entirely through vomiting.

Alsted⁷ reported an elevation in the value for blood urea of more than 39 mg per hundred cubic centimeters in 22 of 26 patients suffering from hematemesis and melena. He found a depression of renal function in 1 patient in whose case the value for blood urea was 216 mg per hundred cubic centimeters. This patient died four days after admission to the hospital, with uremic symptoms but "without any apparent organic renal affection." In 4 other cases in which the blood urea was increased there was no reduction of renal function.

Clausen⁸ noted elevation of the value for blood urea in 3 patients with hematemesis within six to twenty-four hours after the occurrence of hemorrhage, followed by gradual disappearance of the azotemia in the course of a few days. He found no relation between the azotemia and the serum or urinary chlorides. In 2 of the cases in which there were no manifestations of shock, he reported what he interpreted as normal urea clearances, in a third, in which shock was present, he reported a "moderate reduction of the renal function (maximum clearance 29 cc, standard clearance 23 cc) not sufficient to explain the azotemia." He permitted 500 to 600 cc of ox blood to "infuse" into the stomachs of 2 patients and noted an increase in the blood urea of about 25 mg per hundred cubic centimeters within eight hours, with beginning decrease at the end of twenty-four hours.

Borst⁹ found elevation of the urea content of the blood in 5 of 6 patients with peptic ulcer and hematemesis. In 2 of the 5 patients the urea clearance was normal, in 2 others the reduction in clearance to 47 and 58 per cent was not sufficient to account for the increase in urea, whereas in the fifth case there was a reduction to 19 per cent. As there was simultaneous excretion of large amounts of urea in the urine, he felt that elevation of the urea content of the blood was due chiefly to increased breakdown of protein (derived presumably from the blood in the intestinal tract). Although there was a decided increase in the urea

10 Christiansen, T. Biochemical Changes in the Organism Produced by Massive Intra-Intestinal Hemorrhage, *Rev Gastroenterol* 4 166-180, 1937

content of the urine, the proportion of uric acid and creatinine was normal. He also reported increase of the indican content of the blood and of the urine, which he attributed to decomposition of the blood in the intestinal tract.

From the reports of these authors it will be seen that the elevation of the value for urea nitrogen¹¹ which frequently follows hematemesis or melena has been ascribed to a number of factors, namely, dehydration, shock, impairment of renal function, increased catabolism of body protein associated with starvation and absorption of products of decomposition of the blood liberated into the intestinal tract.

We have studied a series of 53 cases of hematemesis or melena observed with 1 exception¹² at the Cincinnati General Hospital since Oct 1, 1937, paying particular attention to the concentration of urea nitrogen in the blood and its relation to clinical findings. In a small group of patients studies of renal function were made, which are to be reported separately. We have been able to confirm the observation that elevation of the urea nitrogen content of the blood following hematemesis may occur in the presence of normal renal function. Studies¹³ have also been made after oral administration of citrated human blood which establish the importance of the quantity of blood present in the intestinal tract at a given time in the production of the increased value for urea nitrogen. In a number of instances the blood chlorides and the carbon dioxide-combining power of the blood were determined and found to be normal.

The determinations of the urea nitrogen content of the blood were carried out in duplicate on oxalated whole blood by means of the aeration method of Van Slyke and Cullen¹⁴. The specimens were obtained immediately after admission of the patient to the hospital before the administration of any food or fluid. In frequent instances the determinations were repeated once or twice daily until the urea nitrogen had returned to a level below 20 mg per hundred cubic centimeters and had remained there for several days or more. Most of the specimens examined later than the day of admission were obtained under fasting conditions, although in some instances the blood was obtained shortly after a meal usually breakfast. It was considered unnecessary to obtain all specimens under fasting conditions because of the fact that single meals con-

11 In some instances it was not clear whether the author was dealing with urea or urea nitrogen, as methods of determination were not given. Some of the very high figures probably refer to values for urea which are 2.14 times those for urea nitrogen.

12 Case 20 was observed at the C. R. Holmes Hospital.

13 Schiff, L., and others. Observations on Oral Administration of Citrated Blood in Man. Effects on Blood Urea Nitrogen, *Am J Digest Dis* 6: 597 (Nov) 1939.

14 Van Slyke, D. D., and Cullen, G. E., in Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 547.

taining a usual amount of protein have only a minor effect on the concentration of urea in the blood (MacKay and MacKay¹⁵) According to Wu,¹⁶ the urea nitrogen content of the blood plasma varies from 13 to 23 mg per hundred cubic centimeters, with an average value of 19 mg According to Berglund,¹⁶ the normal values for whole blood range from 9 to 15 and for blood plasma from 10 to 17 mg per hundred cubic centimeters In a group of 9 controls, from whom blood was taken about two to three hours after a noon meal, we obtained values of 9.6 to 21 mg per hundred cubic centimeters

Immediately after admission to the hospital the patients were placed on a modified Meulengracht regimen similar to that used by Witts¹⁷ Fluids were freely administered either orally or parenterally For the first two days the diet consisted of frequent feedings of egg-nog, milk, cream, toast, pureed vegetables, strained orange juice, butter and water as desired On the third day strained cereal, minced meat and baked or creamed fish were added

The list of cases is given in table 1 In cases in which it is indicated, the cause of hemorrhage seemed reasonably established after clinical study, including roentgen examination, gastroscopic examination and occasionally esophagoscopy examination, biopsy or necropsy It is seen that the value for urea nitrogen may be elevated in a variety of diseases producing hemorrhage from the esophagus, stomach or duodenum, as well as in cases of hemorrhage of undetermined cause

A maximum value for urea nitrogen of 30 mg per hundred cubic centimeters of blood or more was obtained in 36 cases (table 2) The maximum concentration was reached within twenty-four hours of the time of admission in most cases in which patients were seen within three days of the first observation of hemorrhage (table 3)

Elevation of the urea nitrogen content of the blood occurred in the absence of shock (chart 1) No shock was present in 6 of 15 cases in which the maximum concentration was 50 mg per hundred cubic centimeters or higher, in 12 of 24 cases presenting a maximum value of 40 mg or more, and in 22 of 36 cases with a level of 30 mg or more It should be noted, nevertheless, that shock was relatively more frequent in the cases in which the degree of nitrogen elevation was higher, as the figures just cited indicate The criteria of shock were a systolic blood pressure of 90 mm of mercury or less, tachycardia, sweating and pallor

As the level of urea nitrogen in the blood was frequently observed to rise during hospitalization in the presence of adequate administration of fluid it is believed that dehydration can be excluded as an essential fac-

15 MacKay, E. M., and MacKay, L. L. Concentration of Urea in the Blood of Normal Individuals, *J. Clin. Investigation* **4** 295-306, 1927

16 Cited by Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 267

17 Witts, L. J. Haematemesis and Melaena, *Brit. M. J.* **1** 847-852, 1937

TABLE 1—*Fifty-Three Cases of Hematemesis or Melena*

Case No	Age of Patient	Sex of Patient	Probable Source of Hemorrhage	Day of Admission After Hemorrhage	Shock	Minimum R B C, Millions	Minimum Hb, Gm per 100 Cc	Maximum B U N, Mg per 100 Cc
1	65	M	Duod Ulcer†	4	0	13	58	100
2	69	M	Duod Ulcer†	1	0	15	78	43
3	65	M	Duod Ulcer	2	0	30	93	38
4	55	M	Duod Ulcer	1	0	17	62	40
5	50	M	Duod Ulcer	1	+	17	52	56
6	56	M	Duod Ulcer†	1	++	09	40	105
7	40	M	Duod Ulcer	3	0	35	92	25
8	40	M	Duod Ulcer†	9	0	19	50	18
9	40	M	Duod Ulcer†	1	0	23	58	30
10	54	M	Duod Ulcer	1	++	21	58	40
11	34	M	Duod Ulcer	2	0	43	120	19
12	50	M	Duod Ulcer	3	0	22	84	22
13	57	M	Duod Ulcer‡§	12	0	09	32	120
14	36	M	Duod Ulcer	1	0	21	52	43
15	37	M	Duod Ulcer	4	0	10	43	39
16	48	F	Duod Ulcer	5	0	23	52	13
17	45	M	Duod Ulcer	3	0	27	80	35
18	46	F	Duod Ulcer†	1	0	18	60	15
19	26	M	Duod Ulcer†	1	0	11	34	35
20	70	M	Duod Ulcer	1	0	32	105	15
21	53	F	Duod Ulcer	2	0	36	100	36
22	64	M	Gast Ulcer	2	0	17	83	43
23	56	M	Gast Ulcer	3	0	28	83	35
24	34	M	Gast Ulcer	1	0	30	120	50
25	77	F	Gast Ulcer	1	0	15	62	33
26	57	M	Hyp Gastritis	1	++	21	92	64
27	54	M	Hyp Gastritis	1	0	13	46	23
28	35	M	Hem Gastritis†**	7	0	06	24	90
29	60	F	Gast Neuroinoma†	1	0	28	70	37
30	41	F	Gast Carcinoma†	15	0	13	44	26
31	34	M	Gast Lympho sarcoma†	12	0	16	29	20
32	69	M	Esoph Varix†	2	0	22	70	105
33	53	M	Esoph Varix†	1	++	20	60	55
34	55	M	Esoph Varix††	1	++	12	60	105
35	57	M	Ca of pancreas eroding duod †	1	++	13	30	50
36	33	M	Duod Carcinoma†	14	0	18	52	11
37	26	M	Thrombocytopenic purpura	2	++	12	64	38
38	57	M	Ruptured aortic aneurysm†	3	0	19	86	14
39	31	F	Undetermined	1	0	25	68	29
40	52	M	Undetermined	1	+	09	35	40
41	77	M	Undetermined	1	++	33	90	36
42	42	M	Undetermined	2	0	38	130	46
43	62	M	Undetermined	3	+	10	46	43
44	29	M	Undetermined	2	0	08	40	37
45	65	F	Undetermined	8	0	22	60	15
46	52	M	Undetermined	1	0	34	120	38
47	53	M	Undetermined	3	+	11	48	56
48	36	M	Undetermined	4	+	17	52	23
49	50	M	Undetermined	1	+	21	65	65
50	65	F	Undetermined	1	+	11	36	60
51	24	F	Undetermined	2	0	22	82	23
52	79	M	Undetermined†	1	0	32	84	75
53	57	M	Undetermined	1	0	15	60	29

* The patients in cases 7 and 46 were readmitted to the hospital. Data on their cases after the second admission are given under the headings of cases 8 and 47 respectively.

† Necropsy performed

‡ Operation performed

§ Chronic nephritis, necropsy seven months later

** Bacterial endocarditis

†† Died—no autopsy performed

tor in its increase. Two examples are given in chart 2. As the patients were adequately fed, the same would hold true for starvation.

There was no direct relation between the age of the patients and the degree of elevation of the urea content of the blood (chart 3).

A constant relation was not found between the concentration of urea nitrogen and the red blood cell counts. Some relation, however, is suggested between very high concentrations of urea and very low red cell counts, as in 5 of the 6 cases in which the value for urea nitrogen was 90 mg or more per hundred cubic centimeters the red cell count was 1,300,000 or less (chart 4).

TABLE 2—*Maximum Value for Blood Urea Nitrogen in Fifty-Three Cases of Hematemesis or Melena*

Blood Urea Nitrogen, Mg /100 Cc	Number of Cases	Blood Urea Nitrogen, Mg /100 Cc	Number of Cases
100 and above	5	40-49	8
70-99	2	30-39	13
60-69	3	Below 30	17
50-59	5		

TABLE 3—*Day of Maximum Elevation of the Value for Urea in the Blood of Patients Admitted to the Hospital Within Three Days of First Observation of Hemorrhage*

	Maximum Blood Urea Nitrogen (With reference to day after hemorrhage)			
	1st Day	2d Day	3d Day	4th Day
Admitted day of hemorrhage (21)	13	7	1	
Admitted 2d day after hemorrhage (7)		2	2	3
Admitted 3d day after hemorrhage (4)			3	1

* The concentration of urea in the blood at the time of admission to the hospital was 30 mg or more per hundred cubic centimeters.

Repeated determinations of the value for urea were made in the cases of 12 patients who recovered without signs of a second hemorrhage (chart 5). The rapidity with which the blood urea nitrogen may rise after hematemesis is illustrated by case 10. In this case the first hemorrhage occurred during hospitalization, the value for urea nitrogen rising from 21 mg per hundred cubic centimeters twelve hours prior to the hematemesis to 40 mg per hundred cubic centimeters five hours after the hemorrhage. In 6 cases in which the initial determination was made within the first twenty-four hours of bleeding, there was a rather sharp drop within the next twenty-four hours, in 4 there was a rise during the next twenty-four hours followed by a decrease. Whether this secondary rise was due to continued bleeding after admission to the hospital is not known.

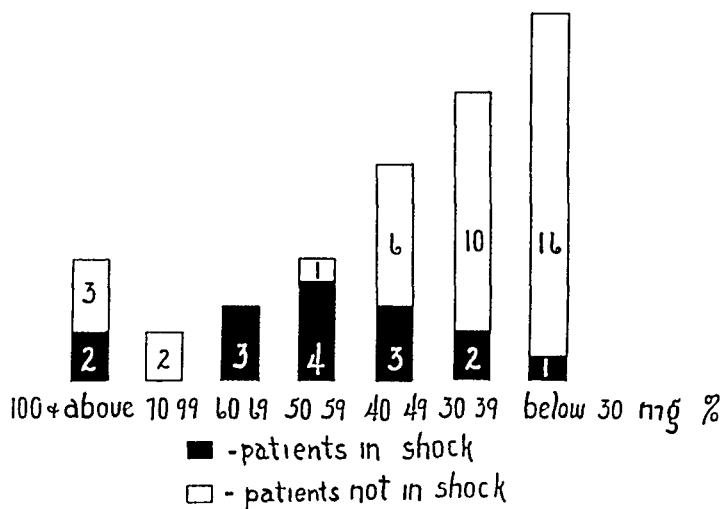


Chart 1—Relation of shock to the maximum value for blood urea nitrogen

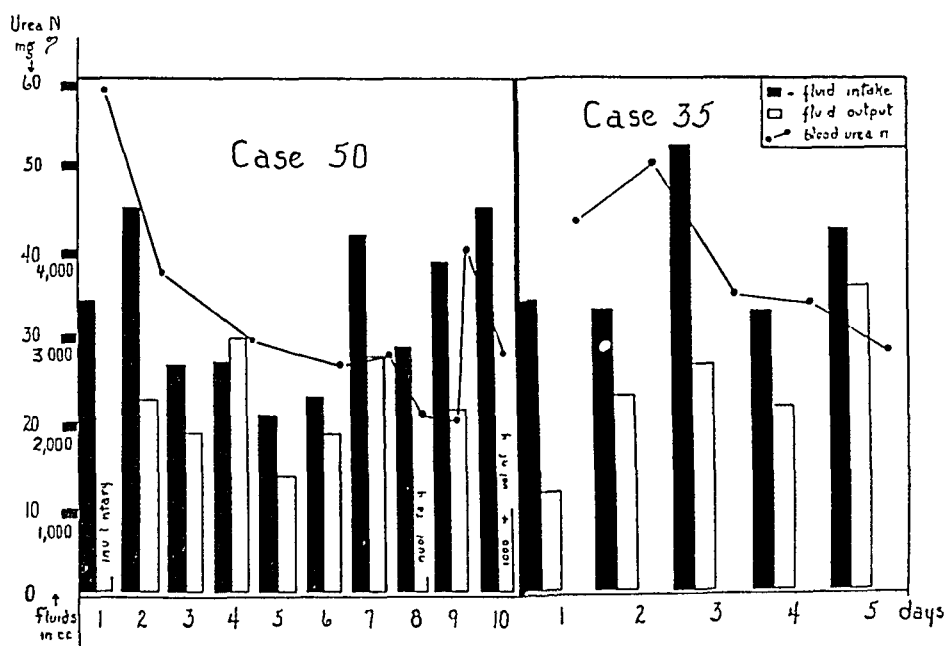


Chart 2—Relation of the urea nitrogen content of the blood to fluid intake and output

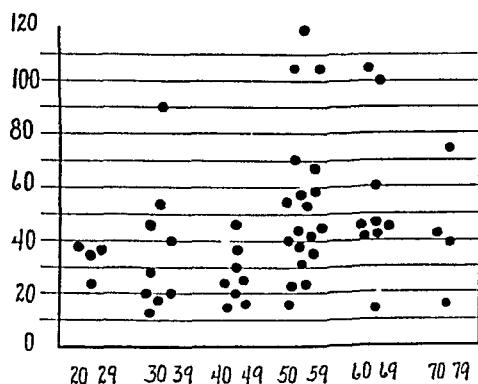


Chart 3—Maximum value for urea nitrogen correlated with the age of the patient

In 5 cases, in which the patients subsequently recovered, further bleeding occurred during observation in the hospital (chart 6), as manifested by hematemesis or by an episode of shock followed by the

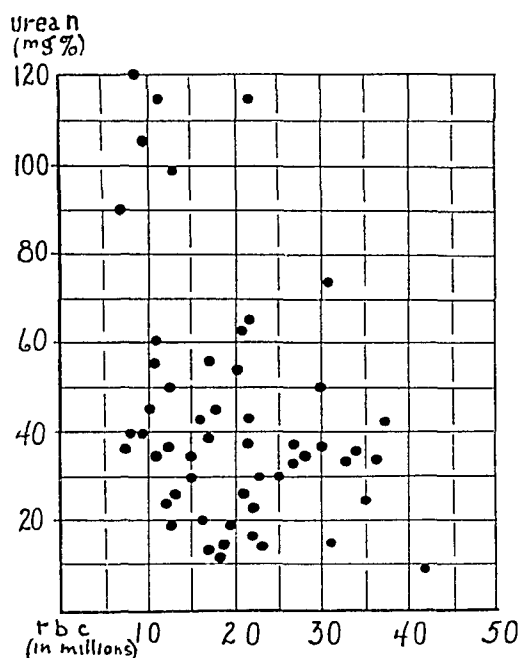


Chart 4—Maximum values for urea nitrogen in the blood and coexistent red blood cell count

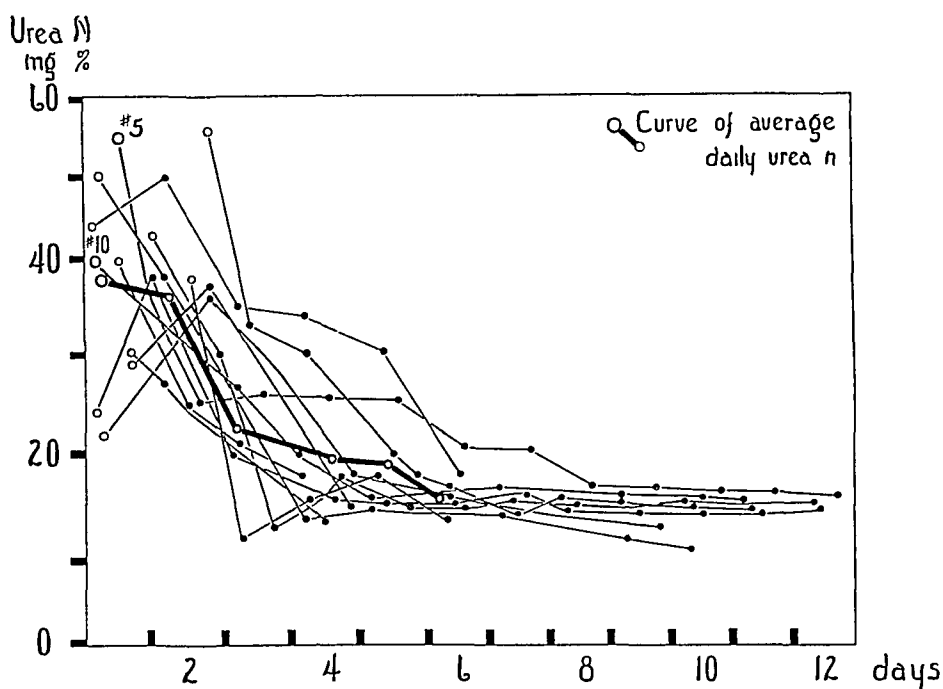


Chart 5—Repeated determinations of the value for blood urea nitrogen in 12 cases of single hemorrhage followed by recovery

passage of tarry stools In 3 of these (cases 4, 43 and 50) there was a prompt rise in the urea nitrogen content of the blood followed by a rather prompt drop to normal by the third day after hemorrhage In

case 17 the urea nitrogen, instead of dropping, remained at almost a constant level for one week, during which there were two episodes of bleeding (There may have been additional occult hemorrhage) In case 26 the value for urea nitrogen sixteen hours after the first hematemesis was 40 mg per hundred cubic centimeters of blood Five hours later a second hematemesis occurred Three hours after this the value for urea nitrogen was 64 mg per hundred cubic centimeters of blood, but it is likely that this increase was an aftermath of the first hemorrhage It should be added that the urea nitrogen was elevated prior to the actual appearance of blood in cases 43 and 50, which suggests

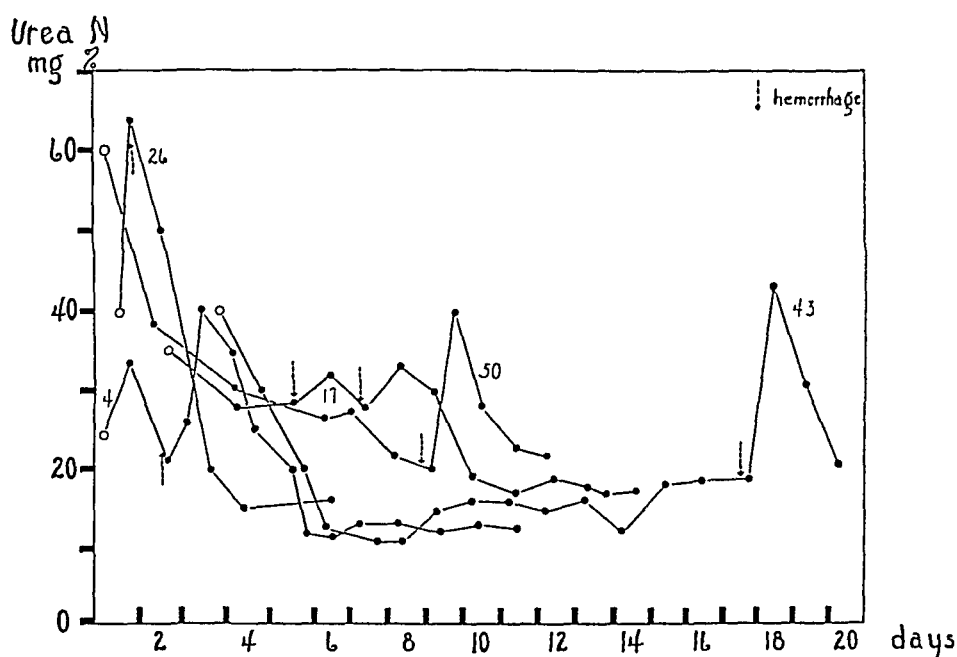


Chart 6—Repeated determinations of the value for blood urea nitrogen in 5 cases of additional nonfatal hemorrhage after admission to the hospital

that determination of the value should prove helpful in the early detection of gastrointestinal hemorrhage

In 8 of the cases in which death occurred opportunity was afforded us to determine the concentration of urea nitrogen in the blood within the first three days of hemorrhage The curves for 7 of the patients are shown in chart 7, the eighth having been excluded because death was due to postoperative pneumonia a month after admission The highest values were obtained in 4 cases (cases 6, 32, 34 and 52), in all of these there was repeated hemorrhage, and varying amounts of blood were found in the gastrointestinal tract in the 3 in which autopsy was done In case 2 there was also repeated hematemesis, yet the urea nitrogen content of the blood, though moderately elevated, decreased

somewhat before death, which occurred thirty-five hours after admission. In case 38, in which bleeding was due to an aortic aneurysm rupturing into the esophagus, a small hematemesis occurred two days before admission and was followed by profuse hematemesis on the day of admission as well as at the time of death, twenty-four hours later. There was practically no old blood in the intestinal tract, which suggested that almost all the blood lost the day before death had been vomited. In case 33, in which there was no bleeding after hospitalization, the urea nitrogen

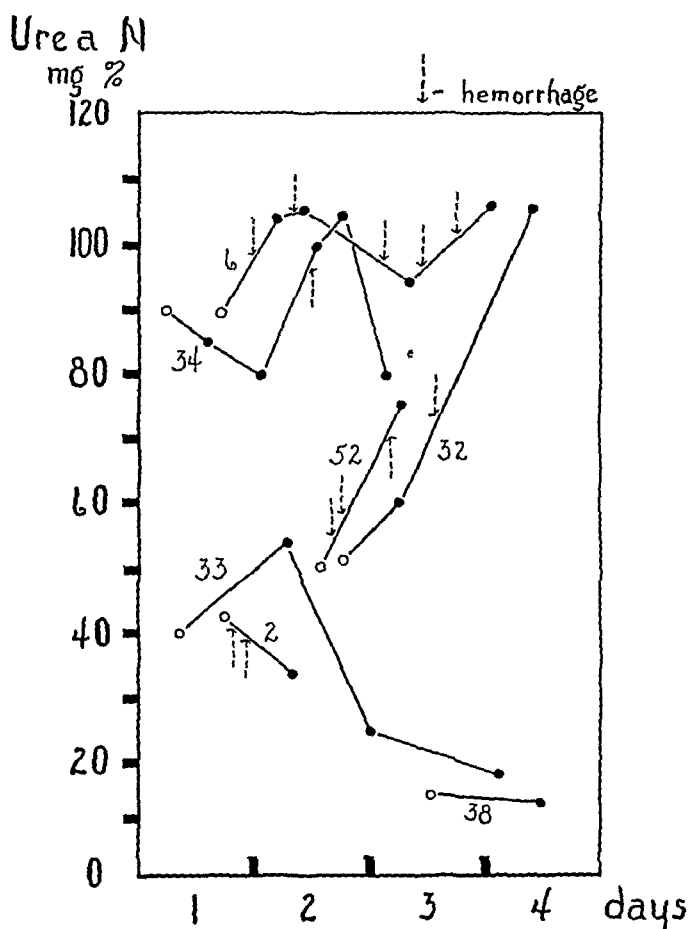


Chart 7—Repeated blood urea nitrogen determinations in 7 cases of fatal hematemesis and melena

curve resembled that seen in the cases of nonfatal single hemorrhage. Death in this case was probably due to hepatic insufficiency.

There was a definite relation between mortality and the degree of elevation of the value for urea nitrogen (table 4). If one excludes those cases in which the primary disease, rather than the hemorrhage it produced, was the cause of death (cases 28, 30, 35, 36 and 38), one finds a fatal outcome in 4 of 5 cases in which there was a value of 100 mg or more, in 5 of 9 cases in which the value was 60 mg or more and in no case in which there was a normal concentration.

It is believed by many that age is the most important single prognostic factor in cases of hematemesis or melena, the mortality of patients over 50 years old being much higher than that of patients below this limit. It is of interest, therefore, to note that in spite of its relation to mortality, there was no direct relation between the concentration of urea in the blood and the age of the patients, as has been indicated.

In view of its relation to mortality, we have, like Witts,¹⁷ come to consider the level of urea nitrogen in the blood as a criterion for blood transfusion and have recently made it a rule to give transfusions in any case in which the value for urea nitrogen after admission rises to 50 mg or more per hundred cubic centimeters of blood. This rule was followed in 9 cases, 6 of the patients recovered. Two of the 3 who died had hepatic cirrhosis.

TABLE 4—*Maximum Values for Blood Urea Nitrogen and Mortality from Hemorrhage in Cases of Hematemesis or Melena (48 Cases*)*

Blood Urea Nitrogen, Mg /100 Cc	Number of Cases	Number of Deaths	Blood Urea Nitrogen, Mg /100 Cc	Number of Cases	Number of Deaths
100 and above	5	4	40-49	8	1
70-99	1	1	30-39	13	0
60-69	3	0	Below 30	14	0
50-59	4	1			

* Cases 28, 30, 35, 36 and 38 have been excluded because of the influence of the primary disease on mortality.

In 17 of the 53 cases the concentration of urea nitrogen in the blood was less than 30 mg per hundred cubic centimeters. These cases, therefore, merit separate consideration. In 9 instances (cases 8, 16, 18, 30, 31, 36, 45, 48 and 51) the first determination was made on the fourth day after the hemorrhage or even later, so that a previous elevation may well have been missed. In 2 cases (39 and 53) the concentration of urea nitrogen might have been considered elevated, since the values in both were 29 mg per hundred cubic centimeters. In 2 other cases (12 and 20) the blood might have been swept through the intestinal tract too rapidly to permit adequate absorption of its decomposition products, a result of a laxative taken at the time of hematemesis. In 1 instance (case 38), the case of ruptured aneurysm, there was no old blood in the intestinal tract. In 3 cases (7, 11 and 27) there was no explanation for the absence of a definite increase.

SUMMARY AND CONCLUSIONS

The urea nitrogen content of the blood is frequently elevated after hematemesis and melena, and the degree of elevation in such instances

is of definite prognostic significance. In cases in which there are a single hemorrhage and subsequent recovery this increase is generally maximal within twenty-four hours (occasionally within forty-eight hours) and is followed by a sharp drop to normal by the third day after bleeding. In cases in which there is a second (nonfatal) hemorrhage there is a secondary increase within twenty-four hours, with a drop to normal by the third day. In cases in which repeated hemorrhages occur and ultimately prove fatal there is an increasingly or persistently high level of urea nitrogen in the blood.

The elevation of the value for urea nitrogen in the blood following hematemesis and melena may occur independently of shock, starvation, dehydration or renal insufficiency. It is not directly related to the age of the patient or to the red blood cell count.

The urea nitrogen content of the blood should be repeatedly estimated in all cases of hematemesis or melena because of its prognostic significance. Its value in prognosis should, in turn, make it an aid to therapeutic management.

Dr. Sander Goodman gave clinical assistance with this work. The translation of Sanguinetti's communications was made by Dr. Louise Cockrell.

INTERCAPILLARY GLOMERULOSCLEROSIS

A SYNDROME OF DIABETES, HYPERTENSION AND ALBUMINURIA

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AND

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In 1936, Kimmelstiel and Wilson¹ reported the pathologic observations in a group of 8 cases of a peculiar renal lesion to which they gave the name intercapillary glomerulosclerosis. On reviewing the clinical records of the cases they found that the observations fell into a fairly well defined symptom complex, consisting of diabetes, albuminuria, hypertension, retinal vascular changes, a more or less well developed nephrotic syndrome and some degree of renal insufficiency. Anson,² in 1938, published a study of the kidneys in the last 900 autopsies at the Hospital of the Medical College of Virginia, he observed 6 cases which satisfied the pathologic criteria proposed by Kimmelstiel and Wilson. Clinically the same features were present as in those of the latter workers, except that the nephrotic syndrome was present in only 2 instances. Neither of these groups of cases was completely studied medically, since a number of the patients were admitted to the surgical wards and others were moribund at the time of admission.

Similar cases have impressed us from the clinical standpoint as instances of peculiarly widespread degenerative vascular disease. In 4 such cases autopsy was performed, the 4 cases are reported in detail in this paper. These and 5 other cases, in which the presence of the lesions of intercapillary glomerulosclerosis was clinically suspected, are analyzed in succeeding paragraphs. Table 1 shows the frequency of the various features of the syndrome in our proved cases and in those of the authors cited.

REPORT OF CASES

CASE 1—J F, a 64 year old American housewife, was admitted to the surgical service Oct 15, 1936 and discharged November 12. An adenocarcinoma of the

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1 Kimmelstiel, P, and Wilson, C. Intercapillary Lesions in the Glomeruli of the Kidney, *Am J Path* **12** 83-98 (Jan) 1936

2 Anson, L J. Intercapillary Glomerulosclerosis, *South M J* **31** 1272-1275 (Dec) 1938

right breast was found, and radical mastectomy was performed. The lymph nodes were not involved. Diabetes had been discovered fifteen years previously and had been controlled by means of diet, insulin being required for only a few weeks postoperatively. The systolic blood pressure ranged between 220 and 180, with the diastolic at 100. There was attenuation of the retinal vessels, and one small round hemorrhage was seen in the left retina. The heart was moderately enlarged to the left. There was no evidence of cardiac failure and no edema. The hemoglobin was 91 per cent. There were 4,200,000 erythrocytes per cubic millimeter of blood. Examination of the urine showed specific gravity, 1.033, albumin, 3 plus, and sugar, complete reduction. The sediment contained occasional pus cells. The nonprotein nitrogen content of the blood was 24 mg per hundred cubic centimeters. Roentgen examination of the chest revealed an enlarged left ventricle. The phenolsulfonphthalein excretion was 58 per cent in two hours.

TABLE 1—*Frequency of Various Symptoms*

Symptoms	All Series (18 Cases)			Kimmelstiel (8 Cases)			Anson (6 Cases)			Present Group (4 Cases with Autopsy)		
	Examined	Found	Percentage	Examined	Found	Percentage	Examined	Found	Percentage	Examined	Found	Percentage
Diabetes	17	17	100	7	7	100	6	6	100	4	4	100
Albuminuria	17	17	100	7	7	100	6	6	100	4	4	100
Retinal changes	8	8	100	1	1	100	3	3	100	4	4	100
Hypertension	17	15	88	7	6	86	6	5*	83	4	4	100
Edema	18	15	83	8	7	88	6	4	67	4	3	75
NPN retention	14	11	79	6	5	83	4	3	75	4	3	75
Hypothenuria (<1.020)	11	7	64	5	3†	60	3	2†	67	3	2	67
Hypoalbuminemia (<2.9%)	6	4	67	0	0		2	1	50	4	3§	75
Heart failure	18	6	33	8	4	50	6	1	13	4	1	25
Anemia	4	1	25	0	0		0	0		4	1	25

* The exception was a patient admitted in shock who never recovered.

† It is not stated whether sugar was present in concentration test specimens. Other patients, therefore, may also have had hypothenuria.

§ Proteins not studied within a year of death in the third case.

The patient was readmitted to the hospital on Dec 28, 1937. She had been treated in the outpatient department for gradually increasing edema which did not respond to digitalization and responded only temporarily to mercurial diuretics, ammonium chloride and urea. Despite a high protein diet the blood proteins fell from 5.15 per cent on May 6 to 4.68 per cent on admission.

Physical Examination—The patient was chronically ill and wasted. She was moderately dyspneic but not orthopneic or cyanotic. No venous engorgement was noted. There was massive edema of the lower extremities and of the right arm. Blurring of the margins of the disks, retinal edema and narrowing and tortuosity of the vessels were present, as were many old and recent hemorrhages, some round and dark, others flame shaped and brighter red. The heart was enlarged to the left. The systolic blood pressure was 230 to 200, and the diastolic, 100. There was evidence of bilateral hydrothorax and of moderate ascites. The edge of the liver was palpated 2 to 4 cm below the costal margin.

Laboratory Examination—The hemoglobin was 77 per cent. There were 4,310,000 erythrocytes per cubic millimeter. Urinalysis showed specific gravity,

1024, albumin, 4 plus, and sugar, 0 The sediment contained occasional pus cells The total protein content of the urine (Kjeldahl) was 13.2 Gm per liter The nonprotein nitrogen content of the blood was 47 and the sugar content (fasting) 135 mg per hundred cubic centimeters

Clinical Course—The aforementioned diuretics were tried again, and thoracentesis was repeatedly performed, but no improvement occurred Transfusions were given and a high protein diet was offered The diet was not well taken by the patient, especially in the last four weeks, when anorexia was marked The level of serum proteins fell to 3.06 per cent (albumin 1.23, globulin 1.70) The patient died of bronchopneumonia on March 16, 1938 One week before death the value for nonprotein nitrogen was only 48 mg per hundred cubic centimeters of blood, and no uremic symptoms were present

Necropsy—The right kidney weighed 200 Gm and the left 190 Gm The thin, translucent capsule stripped with ease, the surface showing numerous small indentations The cut surface showed thinning of the cortex with poor demarcation from the medulla The pelvis and the ureter were not abnormal

Microscopically, the fibrous capsule was thickened and moderately infiltrated by small round cells and plasma cells Some glomeruli were completely hyalinized, practically all the others contained deposits of pink-staining hyaline material between the capillary loops In many places this was seen to extend from the respective vas afferens or efferens in which the wall was hyalinized Where the changes were most marked, the glomeruli consisted entirely of such hyalinized loops The Bowman capsules were thickened in many places, with deposits of the same material, apparently, in layers beneath the epithelium Adhesions between the hyalinized loops and the capsule were occasionally seen The arteriolar walls were thickened, and in places the lumens were extremely narrow

The pancreas and liver were not remarkable Focal pneumonia was present There was generalized arteriosclerosis

CASE 2—V L, a 56 year old Italian laborer, was first observed in the outpatient department on Jan 18, 1928 He had diabetes known to be of two years' duration, which was poorly regulated He complained that he had suffered from epigastric fulness and rare vomiting for an indefinite number of years The systolic blood pressure was 160 and the diastolic 94 The radial arteries were thickened, and the achilles reflexes were absent The urine contained a very slight trace of albumin and completely reduced Benedict's solution The patient was advised to enter the hospital for study and regulation of the diabetes, but he did not return

He was admitted to the hospital six years later Since 1930 he had been treated for diabetes by a private physician, who placed him on a diet and prescribed 10 units of insulin twice a day His weight had been maintained at 135 pounds (61 Kg), but he complained of a return of epigastric discomfort for six months During the two weeks prior to admission, vomiting had been frequent, and gastrointestinal roentgen series revealed marked pyloric obstruction The systolic blood pressure was 170 and the diastolic 110 Many yellowish exudates were present in the ocular fundi, with increased light reflex of the vessels The urine contained albumin (1 plus) but no cells or casts The Kahn test of the serum gave a negative reaction The nonprotein nitrogen content of the blood was 39 mg per hundred cubic centimeters, the serum chlorides 96.8 milliequivalents per liter and the carbon dioxide content 74.8 volumes per cent The value for total protein was 5.90 per cent (albumin 3.98, globulin 1.92), and that for serum cholesterol was 159 mg per hundred cubic centimeters

A partial gastrectomy was performed, after which the patient made an uneventful recovery. The surgical specimen showed a chronic peptic ulcer. The patient was discharged in good condition on Feb 24, 1934.

He was readmitted to the hospital on Nov 11, 1938. In another institution, where he spent five months in 1937 after a hemoptysis, tubercle bacilli had been found in the sputum. He made a good recovery and was discharged with a diagnosis of arrested pulmonary tuberculosis. During the summer and fall of 1938 he suffered repeated infections of the upper respiratory tract and increasing edema, which was only temporarily lessened by the administration of digitalis and urea.

Physical Examination—The patient was wizened and chronically ill. He was lying flat in bed without dyspnea. There was considerable soft edema of all the extremities, the sacrum and the abdominal wall. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 236 systolic and 124 diastolic. Examination of the fundi revealed normal disks, thinned, tortuous vessels with arteriovenous compression and numerous large and small yellowish exudates. One small splinter-like hemorrhage was present. The veins of the neck were not engorged. The lungs were hyperresonant except for dullness over the right base posteriorly. A few rales were heard at both bases. The heart was moderately enlarged to the left. The second aortic sound was tambour-like and split. The edge of the liver could be palpated just below the right costal margin. The prostate was diffusely enlarged to about twice the normal size. There was evidence of extensive peripheral neuropathy in the lower extremities.

Laboratory Examination—The hemoglobin was 78 per cent. There were 4,150,000 erythrocytes per cubic millimeter. Urinalysis showed specific gravity, 1.010 to 1.016, albumin, 2 to 4 plus, and sugar, 0 to 2 plus. The sediment contained rare red blood cells and occasional hyaline and granular casts. The phenol-sulfonphthalein excretion was 13 per cent in two hours. Analysis of the gastric contents revealed no free hydrochloric acid. The congo red test for amyloid disease gave a negative result. The circulation time (dehydrochloric acid, arm to tongue) was 18.5 seconds. The results of chemical examination of the blood are shown in table 2.

Clinical Course—The patient was given a diet high in protein and free from salt. On a regimen of complete rest in bed, digitalis and urea solution, a prompt diuresis occurred. He lost altogether 15 pounds (6.8 Kg) in body weight, and cleared up practically all of the edema. The nonprotein nitrogen content of the blood rose to 129 mg per hundred cubic centimeters during administration of urea and though the level fell somewhat on withdrawal of the drug, it subsequently mounted again. The values for blood chlorides were high throughout, even when 20 Gm of sodium bicarbonate was given daily for a period. General weakness became marked. Intercurrent bronchopneumonia further debilitated the patient. In his final week of life, frequent vomiting necessitated parenteral administration of fluid, by which an effort was made to maintain the electrolytes of the blood at the normal levels. The patient died in uremia on Jan 28, 1939.

Necropsy—The right kidney weighed 155 Gm and the left 145 Gm. The capsule of each was translucent and streaked by dilated capillaries. The capsule stripped with some difficulty, leaving a finely granular surface, yellow-pink and slightly pockmarked. On section the kidney had a waxy, pale appearance. The cortex was thin, being no more than 5 to 6 mm in maximum width. The linear cortical markings were almost obliterated, being replaced by irregular pink streaks and dots. The pelvis and ureter appeared normal.

Microscopically, the entire cortex was diffusely scarred by an increase in fibrous tissue. Practically all the glomeruli had undergone variable degrees of hyaline change. Some were completely hyalinized, others contained deposits of glassy, homogeneous pink hyaline material in smaller amounts, and this lay between the capillary loops. The more severely affected glomeruli had deposits of hyalin in the thickened outer cell layer of Bowman's capsule as well. The afferent arterioles in many instances possessed thickened and hyalinized walls with varying degrees of reduction in the calibers of their lumens. In general, there was thickening of the intima and media with encroachment on the lumens of the smaller arteries. Many of the tubules were collapsed, with patchy infiltrations of lymphocytes about

TABLE 2—*Blood Chemistry (Case 2)*

Date	NPN, Mg /100 Cc	Blood Sugar, Mg /100 Cc	Serum Chlo- rides, Milli equiv- alents	Serum CO ₂ Content, Volume per Cent	Serum Total Protein, Percent age	Serum Albu- min, Percent age	Serum Globulin, Percent age	Comment
1933 11/9	56	200			4.66	2.91	1.75	In dispensary
11/17	129							Urea medication, stopped 11/18
11/21	93		101.5	52.6				Phosphorus 5.66 mg per 100 cc
11/25	89							
11/28	82				5.23	3.90	1.88	Urine protein, 3.1 Gm per liter, 7.1 Gm per 24 hr
12/7	102		105.7	42.6	5.15	3.26	1.89	
12/13	119							
12/23	110		113.9	33.2	5.16	3.03	2.10	Added salt, 5 Gm a day for 4 days
12/27	94	258	109	50.0				Sodium bicarbonate 20 Gm a day for 4 days
1939 1/3	97		111.3	39.1	5.69	3.13	2.56	After transfusion of 525 cc whole blood
1/9	106							Urine protein, 2.5 Gm per liter
1/17	113		105.8	27.6	5.20	3.15	2.05	Icteric index 7 parenteral fluids
1/23	142		105.4	21.7				

them. Some tubules were merely dilated, while in others there was evidence of cellular degeneration.

Generalized arterial and arteriolar sclerosis was present, with the most marked changes in the coronary and renal vessels. There was evidence of both old and recent cardiac infarctions. There was some focal pneumonia. With the exception of a moderate degree of hyalinization of the islets of Langerhans, neither the pancreas nor the liver was remarkable.

CASE 3—S. D., a 69 year old American housewife, was first seen in the outpatient department in 1929, at which time diabetes was discovered and controlled by diet alone.

The first period of hospitalization was from May 10 to June 6, 1934. The patient complained of an ulcer on the right heel, of five months' duration. In addition to the local lesion, findings of note included a blood pressure of 150 systolic and

85 diastolic and sclerosis of the arteries of the retinas and extremities. The Kahn test for syphilis gave a negative result, there was no anemia, and the urine was free of albumin and formed elements.

The second period of hospitalization was from Oct 20, 1936 to Feb 18, 1937. Polyuria had been pronounced for three months, and several ulcers had appeared on the right foot in the previous three weeks. The blood pressure at this time was 195 systolic and 70 diastolic. The heart was moderately enlarged to the left. Pulsations were not felt in the arteries of the lower extremities. Examination of the urine showed specific gravity, 1.014 (maximum), albumin, 2 plus, and sugar, 0. The sediment contained from 0 to 50 pus cells, culture yielded a growth of *Bacillus coli*. The nonprotein nitrogen content of the blood was 32 mg per hundred cubic centimeters. The value for serum protein was 5.57 per cent (albumin 3.17, globulin 2.50). The ulcers healed very slowly. The amount of insulin required varied greatly. Occasional normal blood pressure readings were obtained.

The final admission was on Aug 19, 1938. For the previous four months the patient had suffered from a slowly enlarging painful ulceration on the right fourth toe. For several weeks a crack in the thickened skin of the right great toe had been oozing and occasionally bleeding. During the previous winter she had had several attacks of weakness resulting in falls without loss of consciousness and with full recovery in a day or less on each occasion. For eighteen months increasing dependent edema was noted, largely clearing on rest in bed, and she also complained of diminishing vision, with "spots before the eyes."

Physical Examination—The patient was well preserved. She was without dyspnea or other complaint except local pain in the foot. The fundi showed thinning and tortuosity of the arteries and rare deep hemorrhages. No exudates or blurring was noted. The systolic blood pressure was 205 and the diastolic 100. The heart was slightly enlarged to the left, with accentuation of the aortic second sound. A few rales were heard at the base of the right lung after cough. There was evidence of pulmonary emphysema. The edge of the liver was palpated 2 cm below the right costal margin. The extremities were cool, and there was moderate edema of both legs and feet. Infected ulcers were present on the right foot, with beginning wet gangrene. Arterial pulsations could not be felt in the legs.

Laboratory Examination—The hemoglobin was 95 per cent. There were 5,150,000 erythrocytes per cubic millimeter. Urinalysis showed specific gravity, 1.012, albumin, 3 plus, and sugar, 0. The sediment contained 0 to 20 pus cells per high power field. The blood sugar was 165 and the nonprotein nitrogen 37 mg per hundred cubic centimeters. The serum proteins were not studied.

Clinical Course—The spread of gangrene and the presence of cellulitis and osteomyelitis of the toes necessitated midhigh amputation. Infection of the stump became uncontrollable, and the patient died Oct 2, 1938.

Necropsy—The right kidney weighed 130 Gm and the left 115 Gm. The capsule was thin, stripping readily and revealing a slightly roughened, granular red-brown surface. The cut surface was gray-brown. The cortex was definitely narrowed, and the normal striations were dimly seen. The pelvis, calices and ureter were not abnormal.

Microscopic study revealed a thickened capsule with a moderate amount of round cell infiltration. Some glomeruli were completely hyalinized. Others contained a considerable quantity of pink-staining hyaline material replacing the

capillary loops This material was also seen in the walls of the vasa afferentia and efferentia Some glomeruli contained deposits of pink-staining hyalin between the capillaries The smaller arteries were definitely thickened

The pancreas and liver contained no notable lesions There were a number of old and recent coronary occlusions with myocardial infarcts The amputation wound was suppurative Generalized arteriosclerosis was present

CASE 4—M C, a 57 year old German housewife, was admitted to the hospital in February 1927, complaining of weakness of nine weeks' duration, for which she had consulted a physician, who discovered glycosuria and hypertension Polydipsia had been present for two years, with slight polyuria and no nocturia For the same period the patient had noted occasional numbness of the palms of both hands Except for cough accompanying infrequent infections of the respiratory tract the past history and family history were not contributory

Physical Examination—The patient was flushed She was in no distress, lying flat in bed without dyspnea The temperature was 100.8 F, but the pulse rate and respiratory rate were normal Slight blurring of the disks and moderate arteriosclerotic retinal changes were present The tonsils were large, with some plugs of exudate in their crypts A few rales and bronchovesicular breath sounds were heard over the region of the upper lobe of the right lung The bases were clear The heart was enlarged to the left, with regular rhythm and no murmurs The systolic blood pressure varied from 210 to 154 and the diastolic from 120 to 90 There was no edema The ankle jerks were not obtained

Laboratory Examination—The hemoglobin was 80 per cent There were 5,200,000 erythrocytes per cubic millimeter Examination of urine showed specific gravity, 1.016 (maximum), albumin, 3 plus, sugar, 3 plus, and acetone, 0 The sediment contained an occasional hyaline cast The Wassermann reaction was negative The sugar content of the blood was 177 and the nonprotein nitrogen content 30 mg per hundred cubic centimeters

Clinical Course—The diabetes was easily controlled by diet, with the addition for the first few days of 10 units of insulin The thoracic signs persisted but never became more marked than on admission The patient was afebrile except for a few days and was discharged after three weeks, much improved subjectively and with a gradual fall in the blood pressure to 152 systolic and 88 diastolic

The second admission was in January 1932 In the intervening five years the vision had gradually failed For two years the patient had gradually lost weight and strength, without definite symptoms Eight weeks prior to admission there suddenly developed a productive cough and pain in the right side of the chest, and the patient vomited frequently There was no fever Glycosuria and diabetic symptoms were absent There was almost continuous diarrhea, with six to ten watery stools daily throughout this period Epigastric soreness was present for two days

Physical Examination—The patient was cachectic, dehydrated and pallid The respirations were shallow but not rapid The temperature was 97 F and the pulse rate 90 The tongue was reddened and smooth The pulmonary signs were those of extensive bilateral pneumonic involvement The edge of the liver was firm and extended 3 cm below the costal margin Slight edema of the legs was noted There were bilateral incipient cataracts, obscuring the fundi, on the left, however, a large organized hemorrhage could be seen

Laboratory Examination—The hemoglobin was 53 per cent There were 3,200,000 erythrocytes and 5,700 leukocytes per cubic millimeter The blood smear

gave evidence of hypochromic anemia. Examination of the urine showed albumin 4 plus and sugar 0. Examination of the sediment gave negative results. The sugar content of the blood was 129 and the nonprotein nitrogen content 58 mg per hundred cubic centimeters. The total protein content of the serum was 4.94 per cent (albumin 2.34, globulin 2.60). The sputum contained many acid-fast bacilli. Roentgenograms of the lungs revealed extensive tuberculous infiltration, with a cavity in the upper lobe of the right lung.

Clinical Course—The diarrhea responded to administration of camphorated tincture of opium U. S. P. Dehydration was combated by parenteral administration of fluids. Marked generalized edema promptly developed, persisting to the time of the patient's death in stupor three weeks after admission.

Necropsy—Each kidney weighed 125 Gm. The capsule stripped with difficulty and revealed a granular yellow-brown surface. The cortex was of usual thickness and was yellow-brown as contrasted with the grayish medulla. The vessels stood out in cut section and were narrowed. A thrombus almost occluded the left renal vein. The pelvis and ureter were normal.

On microscopic examination the capsule was seen to be slightly thickened. A large number of glomeruli were seen to be composed of groups of hyaline deposits. Others contained only two or three capillary loops embedded in hyaline intercapillary material, while many other glomeruli had a few deposits of this material between the capillaries. The arterioles were moderately thickened. A small amount of amyloid was seen in a few glomeruli. It had not the distribution of the hyaline material described.

The pancreas was not unusual. The liver contained a few tubercles. There was extensive pulmonary and intestinal tuberculosis. Acute vegetative endocarditis was present on the aortic valve. There was a considerable degree of generalized arteriosclerosis.

PATHOLOGIC PICTURE

The kidneys in all 4 cases showed the typical lesions described by Kimmelstiel and Wilson.¹ Special staining methods were not applied to the sections except such as were necessary to disclose amyloid deposits. Many glomeruli in each case³ were hyalinized completely (fig 1) or in part, with the hyalin confined to the centers of the glomeruli or of the individual lobules (fig 2). In this condition the number of capillaries of the involved glomeruli is apparently reduced, often but a ring of open capillaries surrounds the hyaline mass, which consists of a broadening of the intercapillary connective tissue, best seen at the hilus. A high degree of arteriosclerosis with fatty degeneration of the arterioles is present, in many cases overshadowing the specific lesions. The hyaline degeneration may be seen in some cases to extend from the vasa afferentia into the intraglomerular mass. The capillary walls are thickened. Those at the center seem to merge with the hyaline mass and collapse, their nuclei becoming embedded in the mass. They are seen to be in various stages of necrobiosis and may assume an onion peel arrangement about the central hyalin. The capsular changes consist of deposits

3 Except in case 2, in which fewer lesions were seen. Extensive vascular changes in the kidneys in this case masked the picture to some extent.



Fig 1 (case 1) —A glomerulus partly involved $\times 250$

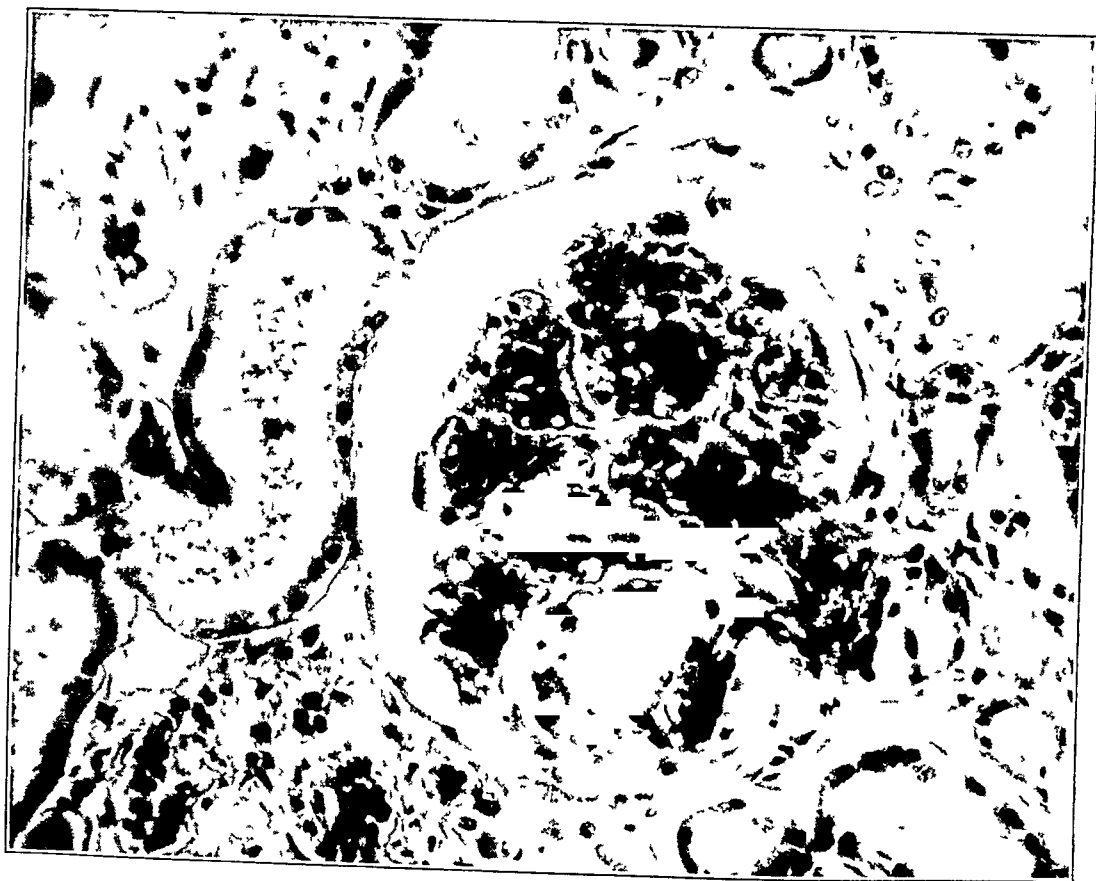


Fig 2 (case 1) —A glomerulus markedly involved $\times 250$

of hyaline material and lipoid beneath the epithelium Kimmelstiel and Wilson have demonstrated by stains of the basement membrane that these deposits are laid down between the basement membrane and the epithelium Tubular changes were inconstant, consisting mainly of fat deposits in the tubular epithelium Nephrosclerotic changes were constantly present

Kimmelstiel and Wilson pointed out the differences between the lesions described and those of intracapillary and of extracapillary glomerulonephritis A stage exists in both these conditions in which similar lesions of the intercapillary connective tissue are observed However, in these other types of glomerular disease, the marked changes in the basement membrane serve as the differential point

CLINICAL FEATURES

The following discussion of the clinical phenomena associated with intercapillary glomerulosclerosis is based on our 4 cases in which autopsy was done and on 5 additional cases which were characteristic clinically Two of the patients in the latter cases have died, but autopsies were not performed The others are still living at the time of this report Occasionally cases from the series collected by Kimmelstiel and Wilson¹ and by Anson² will be cited, but these are less useful for our purposes because of the sketchy nature of the case reports

In general, it is of considerable interest that the patients presented many of the features of malignant hypertension (nephrosclerosis) The presence of hypertensive neuroretinopathy is stated by Fishberg⁴ to be of ominous prognostic import, most patients with this symptom dying within a year Even arteriosclerotic changes influence the prognosis unfavorably, although in diabetic persons this is of less significance Profuse albuminuria, marked hypertension and evidence of renal decompensation individually would shorten the expectancy of life Yet many patients have lived for a considerable period with most or all of these signs

Age—One patient in Anson's series was 35, but all the others of the combined groups were over 40 at the time of onset of the diabetes, albuminuria, or both

Sex—Of our 7 patients, 5 were women Nine of the 16 others were women

Diabetes—This condition was present in all cases in the entire group and was not ruled out in the 1 exception in Kimmelstiel's group, in which the patient died before laboratory studies could be done The

⁴ Fishberg, A. M. Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 694

disorder was mild, usually requiring little or no insulin for control except when an infection supervened, in no instance did the diabetes appear to influence the progress of the disease. It is not unlikely that cases will be observed in which the diabetes is latent or even in which sugar tolerance is not decreased. Impairment of this function in patients with idiopathic hypertension, especially older persons, is well known.⁵ Many of our patients have had hypertension at the time of discovery of the diabetes. One, however, who has had albuminuria and diabetes for sixteen years, had a normal blood pressure up to four years prior to the time of this report.

Albuminuria—Albuminuria is considered an essential part of the syndrome and was present in varying degree in all cases. While it is usually profuse and is always so terminally, 1 patient had only a slight degree of albuminuria up to within a year of death, at which time a full-blown nephrotic syndrome developed. The early presence of albuminuria is of considerable significance from a diagnostic standpoint and may have a bearing on the pathogenesis of the disease.

Retinal Changes—Arteriosclerotic changes in the retinas were present in all cases, in addition, papilledema, fresh hemorrhages and exudates characteristic of the malignant phase of hypertension were present in 5 instances. One patient had repeated hemorrhages and exudates in the macular regions, causing transient amauroses and progressive diminution of vision. Vision was seriously impaired by similar lesions in 2 other cases. Another patient, excluded from this series only because of the presence of a normal value for serum albumin, also went on to blindness owing to repeated retinal hemorrhages. Immature cataracts were present in 3 patients. It is of considerable interest that hypertensive changes, usually considered to be of ominous import, were present from two to five years in 4 of our patients who had these lesions.

Hypertension—This condition was present for varying periods in all of the cases and was usually of considerable duration, being found on the first examination of all but 1 patient (the man mentioned previously, who had diabetes and albuminuria for sixteen years but hypertension for only four years). In 5 cases the systolic pressure exceeded 200 mm. of mercury, in 1 it exceeded 250. The presence of myocardial fibrosis due to coronary occlusion often results in a lowering of the blood pressure as it may have in 1 of Anson's cases. Patient M. C. (case 4) in our series had hypertension at the time of her first admission to the hospital, five years before death, and a normal blood pressure at a single examination in her final weeks, by which time extensive disseminated tuberculosis had developed.

⁵ Herrick, W. W. Hypertension and Hyperglycemia, J. A. M. A. **81** 1942-1944 (Dec. 8) 1923

Edema—Some degree of edema was present in the entire group and was well marked in 7 of the 9 cases. It was inversely proportional to the level of serum albumin, which in turn depended on the severity of the albuminuria and on the protein intake. In case 1, owing to a level of protein of 13.2 Gm per liter of urine, there was a rapidly falling value for serum albumin in spite of a good protein intake.

Heart Failure—Heart failure, when present, was mainly left sided, on a hypertensive basis, the heart failure on the right side was not proportional to the degree of edema. In 2 cases venous pressure and circulation time from the arm to the tongue were measured and found to be normal or only slightly elevated. Circulatory failure was the terminal event in 1 case.

Hyposthenuria and Nitrogen Retention—These conditions were commonly found in our group, concentrating ability being moderately impaired in all cases and markedly so in 5, the nonprotein nitrogen content of the blood was elevated in all but 2 cases. None of our patients lived over a year with elevated values for nonprotein nitrogen, but there are too few cases in the series to warrant deductions as to the prognostic significance of nitrogen retention.

Anemia—Hypochromic, normocytic or microcytic anemia was present in 4 of the patients, all of whom had nitrogen retention. The anemia, presumably on a renal basis, was characteristically unresponsive to iron therapy.

COMMENT

A consideration of the clinical findings and postmortem observations in a total of 18 cases presenting similar features and a characteristic lesion, together with 5 others without autopsy, seems to warrant grouping them together as falling into a distinctive disease picture, of which the constant features are diabetes, albuminuria, hypertension and retinal vascular changes. The nephrotic syndrome is common and depends for its development on the extent and duration of the albuminuria and the protein intake. Fishberg,⁴ recognizing some of the clinical features of intercapillary glomerulosclerosis, emphasized the latter point.

The pathogenesis of this condition appears to depend on severe and extensive arterial and arteriolar degeneration, associated with and perhaps resulting in diabetes mellitus, hypertension and renal damage.

Differential diagnosis requires the exclusion of amyloid disease coincident with diabetes and hypertension, which rare combination might conceivably reproduce this syndrome. Patient M. C. (case 4) had slight amyloid changes in the kidneys and spleen, not sufficiently marked to account for the clinical picture. The nephrotic stage of chronic glomerulonephritis in association with diabetes usually occurs in a younger age group, and the history is often characteristic. In 1 case mentioned

by Kimmelstiel and Wilson but not included in their series, the picture was indistinguishable both clinically and pathologically from that of intercapillary glomerulosclerosis, since lesions both of the latter condition and of glomerulonephritis were present

A search through the pathologic material of the New Haven Hospital revealed none of the characteristic renal lesions in 170 assorted cases, including cases of diabetes, hypertension, arteriosclerosis and various types of nephritis, with the exception of 1 case of subacute glomerulonephritis in a boy aged 14 who did not have diabetes or widespread vascular disease but who had a few suggestive intercapillary glomerular lesions. Special stains of the basement membrane were not done

SUMMARY AND CONCLUSIONS

A group of 4 cases in which the lesions of intercapillary glomerulosclerosis were observed at autopsy is reported in detail, and the clinical findings in this and in two previously reported series are tabulated

Five other cases in which intercapillary glomerulosclerosis was clinically suspected are analyzed

The pathologic picture is described, and the reasons for considering intercapillary glomerulosclerosis a disease entity are discussed

Dr. H. Arnold reviewed the pathologic material

PHYSIOLOGIC BASIS OF INTRAVENOUS DEXTROSE THERAPY FOR DISEASES OF THE LIVER

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Since Rosenbaum,¹ in 1882, called attention to the depletion of hepatic glycogen following chloroform narcosis, arsenic or phosphorus poisoning and excessive administration of morphine, there has been adequate confirmation of the fact that a damaged liver contains little glycogen.² Concomitant with the loss of glycogen, fatty changes appear in the liver after exposure to these hepatotoxic agents. Rosenfeld³ observed that animals fed carbohydrate are, in general, less susceptible to any drug which produces accumulations of fat in the liver. Furthermore, after such poisonings the feeding of dextrose aids recovery of the animal. Since the early reports of Whipple and Sperry,⁴ Opie and Alford⁵ and Graham⁶ on the resistance to chloroform or phosphorus poisoning of animals fed large amounts of carbohydrate or animals with livers containing large stores of glycogen, there have been many

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similar observations.⁷ The protective action of high carbohydrate intake has also been noted in the prevention of hepatic damage following experimental ligation of the common bile duct,⁸ operation for Eck fistula,⁹ partial hepatectomy¹⁰ and experimental poisoning with the mushroom *Amanita phalloides*.¹¹

The various demonstrations of the life-saving action of high carbohydrate intake on animals with experimentally damaged livers have been paralleled by clinical exploations of the therapeutic and prophylactic possibilities of administration of dextrose to patients with diseases of the liver.¹² The earlier clinical work was lacking in striking results

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11 Steinbrinck, W. Ueber klinische und experimentelle Beobachtungen der hypoglykämischen Reaktion bei Leberparenchymschädigungen, *Klin Wchnschr* **3** 1029, 1924

12 (a) Althausen, T. L. Dextrose Therapy in Diseases of the Liver, *J A M A* **100** 1163 (April 15) 1933 (b) Baehr, G., and Klemperer, P. Degenerative and Diffuse Inflammatory Diseases of the Liver, *Internat Clin* **2** 107, 1929 (c) Butt, H. R. Common Emergencies Arising in the Course of Hepatic Disease, *M Clin North America* **22** 967, 1938 (d) Jacoby, H. G. Glucose Tolerance as a Diagnostic Aid in Jaundice. III. Toxic Hepatitis, *Am J Digest Dis & Nutrition* **4** 162, 1938 (e) Jones, C. M. The Treatment of Acute Hepatic Insufficiency and Its Relation to Prognosis, *ibid* **3** 624, 1936 (f) Kehr, H. Die gut und bosartigen Neubildungen der Gallenblase und der Gallengänge unter besonderer Berücksichtigung eigener Erfahrungen, *Ergebn d Chir u*

because of general failure to use sufficiently large amounts of carbohydrate. The recent experimental results obtained by Bollman and his co-workers have emphasized the therapeutic possibilities when adequate carbohydrate is administered.¹³ On the basis of Rosenbaum's observations and Rosenfeld's theories, Beddard,²¹ as early as 1908, had suggested that dextrose be used clinically in large quantities to restore the depleted reserves of hepatic glycogen in cases of delayed poisoning after chloroform anesthesia. In addition to administration of dextrose by mouth and by rectal enemas, Beddard advised the clinical intravenous use of a 6 per cent solution. It is only recently, however, that the general introduction of adequate dextrose therapy for hepatic diseases has been shown to produce a definite decrease in mortality. In a series of cases in which acute hepatic insufficiency was treated with varying amounts of carbohydrate given by mouth and intravenously, Jones^{12c} found that in a group of 10 cases observed from 1922 to 1925, in which the patients were given a diet low in fat and supposedly high in carbohydrate, the mortality was 90 per cent. In only 2 instances was dextrose administered intravenously. In the next five years, with diets somewhat higher in carbohydrates (300 to 400 Gm daily) but with intravenous administration of dextrose in only 4 instances, there was 100 per cent mortality in 14 cases. However, in the years 1930 to 1935, when dextrose therapy was vigorous, 32 patients were treated with diets containing 400 to 500 Gm of carbohydrate daily, 26 of them receiving dextrose intravenously and the mortality was lowered to 63 per cent. This author concluded: "The more intensive the glucose therapy, the better the prognosis."

This empiric finding has its rational basis in what is now known concerning the homeostatic mechanism of the liver. The work of Mann¹⁴ and of Soskin¹⁵ has shown that the liver is the sole source of the blood sugar. When the intact animal receives dextrose parenterally or via the gastrointestinal tract in sufficient amounts to raise the concentration of dextrose in the afferent hepatic blood above a definite threshold, the production of blood dextrose by the liver is suppressed. This mechanism was postulated by Soskin, Allweiss and

Orthop **8** 471, 1914. (g) Snell, A. M. The Treatment of Liver Disease, *Ann Int Med* **12** 592, 1938. (h) Tallqvist, T. W. Ueber die Beeinflussung des Eiweissumsatzes durch Fette und Kohlehydrate bei einigen Leberkrankheiten, *Arch f Hyg* **65** 39, 1908. Beddard²¹ Steinbrinck¹¹

13 Bollman, J. L. Experimental Studies on Hepatic Alterations, *Proc Staff Meet, Mayo Clin* **11** 727, 1936, footnotes 7 b and 8 a. Bollman and Mann^{8b}

14 Mann, F. C. The Effects of Complete and of Partial Removal of the Liver, *Medicine* **6** 419, 1927.

15 Soskin, S. Muscle Glycogen as a Source of Blood Sugar, *Am J Physiol.* **81** 382, 1927.

Cohn¹⁶ from a consideration of the concentration of dextrose in blood entering and leaving the liver during dextrose tolerance tests. It was substantially confirmed by Tsai and Yi¹⁷ and later was directly demonstrated by Soskin and his co-workers,¹⁸ who calculated the amount of sugar entering and leaving the liver with the aid of thermistor-muhr measurements of blood flow. It was demonstrated also¹⁶ that the response of the liver is not dependent on any extra secretion of insulin from the pancreas but is dependent on the presence of an optimal amount of circulating insulin. The decreased supply of sugar to the blood by the liver during hyperglycemia of exogenous origin is accompanied by an increase in the stores of hepatic glycogen. This hepatic mechanism for regulating the level of blood sugar has been compared to a thermostat-furnace combination.¹⁹ In this analogy the room temperature is equivalent to the blood sugar level and the thermostat-furnace corresponds to the liver. With a sudden increase in the temperature of the room, the thermostat shuts the furnace off. The drop in the room temperature back to normal is chiefly due to the cessation of heat supply from the furnace, although some increase occurs in the dissipation of heat from the room. If on such an occasion one were to follow the room temperature closely one would see first a rise to and a little above the critical level of the thermostat, then a fall back to the previous constant level, with perhaps a little swing below normal, depending on the characteristics of the particular thermostat. This curve of rise and fall is analogous to the normal dextrose tolerance curve, when the influx of exogenous sugar into the blood stream causes the liver temporarily to cut off its supply of sugar to the blood.

There is evidence that one of the first effects of hepatotoxins is to act as mutants to the glycogenolytic mechanism of the liver.²⁰ To return to the analogy, the thermostat has been damaged and no longer reacts sensitively to its usual stimulus. Greater hyperglycemia, there-

16 Soskin, S., Allweiss, M. D., and Cohn, D. J. Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve, *Am J Physiol* **109** 155, 1934.

17 Tsai, C., and Yi, C. L. Carbohydrate Metabolism of the Liver. III. The Sugar Intake During Glucose Absorption, *Chinese J Physiol* **8** 273, 1934.

18 Soskin, S., Essex, H. E., Herrick, J. F., and Mann, F. C. The Mechanism of Regulation of the Blood Sugar by the Liver, *Am J Physiol* **124** 558, 1938.

19 Soskin, S., Allweiss, M. D., and Mirsky, I. A. (a) The Mechanism and Treatment of "Insulin Resistance" and Related Conditions, *J A M A* **108** 504 (Feb 6) 1937, (b) Interpretation of Abnormal Dextrose Tolerance Curves Occurring in Toxemia in Terms of Liver Function, *Arch Int Med* **56** 927 (Nov) 1935.

20 Althausen, T. L., and Thoenes, E. Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes. II. Phosphorus Poisoning, *Arch Int Med* **50** 58 (July) 1932. Soskin and others^{19b}

fore, is necessary to suppress the supply of blood sugar and to favor deposition of glycogen in an acutely damaged liver than in a normal liver. However, when the blood sugar is raised to a sufficiently high level, the damaged liver does respond like the normal by ceasing to supply blood sugar.²¹ The benefit derived from a decrease in the sugar-forming activity of the damaged liver may be regarded as equivalent to the favorable therapeutic results obtained by limiting the activity of other damaged tissues and organs in order to facilitate recovery and repair. The mechanism by which the "resting" or "splinted" liver is able to resist damage more effectively than the active or hyperactive liver is still unknown. The fact that many toxic substances are excreted as glucuronates²² suggests that excessive stores of carbohydrate favor detoxification.

It is now generally accepted that acute and chronic destructive or degenerative processes of the hepatic parenchyma are best treated with large amounts of carbohydrate. A difference of opinion exists, however, concerning the advantages of intravenous administration of dextrose if the patient can take the necessary dextrose or carbohydrate by mouth.²³ The necessary amount of carbohydrate is supplied by the amount of dextrose sufficient to raise the blood sugar to a level which will suppress the output of hepatic sugar. Whereas the normal liver will respond to the usual postprandial hyperglycemia, the "irritable" liver associated with acute toxemia may require a much higher concentration of blood sugar to inhibit the formation of hepatic sugar. That this is so is seen in the prompt response of the acutely poisoned liver in curtailing its output of sugar when large doses of dextrose are given intravenously, small doses having little or no effect.²¹ Furthermore, as Cori and Cori²⁴ have pointed out concerning the normal liver, "the blood sugar concentration and not the amount of glucose administered must be regarded as important for the rate of glycogen deposition in the liver." Consequently, when an attempt is made to protect a damaged liver by means of deposition of glycogen therein, the blood sugar concentration may have to be raised to a level which it may be impossible to obtain by feeding carbohydrates. In such a case intravenous infusion

21 Soskin, S., and Mirsky, I. A. The Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve, *Am J Physiol* **112** 649, 1935.

22 Sauer, J. Die quantitative Glykuronsauerbestimmung im Harn ist eine Leberfunktionsprüfung, *Klin Wchnschr* **9** 2351, 1930. Bollman^{8a}

23 Althausen, T. L., and Stockholm, M. Deposition of Glycogen in Normal and in Experimentally Damaged Livers After Oral and Intravenous Administration of Dextrose, *Am J Digest Dis & Nutrition* **4** 752, 1938. Althausen^{12a} Snell^{12g}

24 Cori, C. F., and Cori, G. T. The Influence of Insulin and Epinephrine on Glycogen Formation in the Liver, *J Biol Chem* **85** 275, 1929-1930.

of dextrose is essential. The fact that extreme hyperglycemia so produced may result in glycosuria should not deter one from such vigorous therapy.

Because of the glycosuria which may result from intravenous dextrose therapy, some physicians favor the routine use of insulin with the sugar. However, it should be pointed out that unless the patient is diabetic the indiscriminate use of insulin may defeat the very purpose of the administration of dextrose. We have already referred to the evidence that in the presence of sufficient insulin to maintain a normal constant blood sugar level no additional insulin is necessary to obtain a normal hepatic response to administered sugar.¹⁶ The injection of insulin into a nondiabetic person can, therefore, produce no additional hepatic effect but does cause increased storage of glycogen in the muscles. This peripheral effect causes a fall in the level of blood sugar, which in turn stimulates the liver to pour out more sugar. The liver is deprived of glycogen rather than replenished with it. Maintaining the hyperglycemia in spite of the administered insulin will prevent this reversal in effect but will not be more beneficial than the same amount of sugar without insulin. Soskin, Allweiss and Minsky¹⁹ have shown that the use of insulin with dextrose in the treatment of toxic nondiabetic animals shortens life, animals receiving dextrose alone live longer.

After prolonged intravenous injections of dextrose designed to suppress the sugar-producing mechanism of the liver, the organ requires an interval to recover from the inhibition of dextrose formation, so that hypoglycemia may appear one to three hours after the cessation of the infusion.²⁵ This should be anticipated and treated with small doses of carbohydrate given by mouth, or intravenously if necessary.

²⁵ Soskin, S, and Allweiss, M. D. The Hypoglycemic Phase of the Dextrose Tolerance Curve, *Am J Physiol* **110** 4 1934

STUDIES ON DESTRUCTION OF RED BLOOD CELLS

I CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA AN INVESTIGATION OF THE MECHANISM OF HEMOLYSIS, WITH OBSERVATIONS ON FIVE CASES

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The disease syndrome of chronic hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria was described as a separate entity in 1928 and 1931 by Marchiafava¹ and in 1931 by Micheli². The clinical manifestations have been reviewed recently with the report of cases by Witts³ and by Hamburger and Bernstein⁴. The pathologic observations in 2 cases, with a review of the literature, were reported in 1938 by Scott, Robb-Smith and Scowen⁵. Van den Bergh⁶ in 1911 made important observations on the in vitro manifestations of this disease without distinguishing it from acholuric hemolytic jaundice. A preliminary report on the mechanism of hemolysis was published in 1937 by Ham,⁷ these observations were confirmed in 1938 by Dacie

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1 Marchiafava, E. Anemia emolitica con emosiderinuria perpetua, *Polislinico (sez med)* **35** 105, 1928, **38** 105, 1931

2 Micheli, F. Anemia (splenomegalia) emolitica con emoglobinuria-emosiderinuria tipo Marchiafava, *Haematologica*, I Arch **12** 101, 1931

3 Witts, L. J. Paroxysmal Haemoglobinurias, *Lancet* **2** 115, 1936

4 Hamburger, L. P., and Bernstein, A. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, *Am J M Sc* **192** 301, 1936

5 Scott, R. B., Robb-Smith, A. H. T., and Scowen, E. F. The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Haemolytic Anaemia, *Quart J Med* **7** 95, 1938

6 van den Bergh, A. A. H. Ictère hémolytique avec crises hémoglobinuriques. Fragilité globulaire, *Rev de méd* **31** 63, 1911

7 Ham, T. H. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria. A Study of the Mechanism of Hemolysis in Relation to Acid-Base Equilibrium, *New England J Med* **217** 915, 1937

Israels and Wilkinson⁸ Jordan⁹ in 1938 published independent observations on the hemolytic mechanism

The present communication deals with the relation of the acid-base equilibrium of blood to hemolysis in vivo and in vitro and with observations on certain features of the mechanism of destruction of red blood cells. Summaries are presented of the clinical and laboratory findings in 4 unreported cases, and observations on 1 case reported previously by Hamburger and Bernstein⁴ are included. Another communication^{9a} will deal with certain immunologic aspects of the hemolytic system in this disease.

MATERIAL AND METHOD

(a) *Quantitative Estimation of Hemoglobin in Plasma and in Urine*—The benzidine method of Bing and Baker¹⁰ was modified for the estimation of the concentration of hemoglobin in the plasma and in the urine. Venous blood was collected with a syringe and needle rinsed three times in 0.85 per cent sodium chloride solution and was then mixed with 10 per cent (by volume) of 3 per cent sodium citrate solution as an anticoagulant. To prevent hemolysis from manipulation of blood, only those samples were examined which were obtained by an uncomplicated venipuncture with a ready flow of blood. All samples were handled with a minimum of agitation. The specimen was centrifuged immediately, and the supernatant plasma was stored at ice box temperature. For estimation of hemoglobin, samples of from 0.05 to 0.2 cc of plasma were introduced into 2 cc of benzidine solution and the color reaction observed as described by Bing and Baker. The result was corrected for dilution of plasma by the anticoagulant. This method was sensitive and moderately accurate for concentration of hemoglobin as low as 20 mg per hundred cubic centimeters of plasma. The concentration of hemoglobin in plasma from normal subjects collected with the aforementioned precautions was usually a trace and always less than 5 mg per hundred cubic centimeters. A standard hemoglobin solution was prepared by diluting 1 cc of venous blood to 2 liters with distilled water; the concentration of hemoglobin in the sample of venous blood was determined by the oxygen capacity method of Van Slyke¹¹. Urine was collected daily in individual specimens under toluene and pooled for two periods of twelve hours each, the period from 9 p m through 9 a m representing the sleeping period and that from 9 a m through 9 p m the waking period. For estimation of the hemoglobin content, samples of 0.05 to 0.2 cc of urine were added to 2 cc of benzidine solution, the same volume of normal urine was added to the sample containing the hemoglobin standard.

8 Dacie, J. V., Israels, M. C. G., and Wilkinson, J. F. Paroxysmal Nocturnal Haemoglobinuria of the Marchiafava Type, *Lancet* **1** 479, 1938.

9 Jordan, F. L. J. Etudes sur l'hémoglobinurie, *Acta med Scandinav* **95**: 319, 1938.

9a Ham, T. H., and Dingle, J. H. Studies on Destruction of Red Blood Cells. II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria. Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum Complement, *J. Clin. Investigation*, to be published.

10 Bing, F. C., and Baker, R. W. Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method, *J. Biol. Chem.* **92** 589, 1931.

11 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

The addition of urine to benzidine caused variable precipitation of the reagent because of the salt concentration. This method as employed for urine, therefore, provided only a crude estimation of the hemoglobin concentration.

(b) *Hemolysis Test with Acidified Serum*—The *in vitro* hemolysis test with acidified plasma or serum was performed on red blood cells washed three times in physiologic solution of sodium chloride and made to a 5 or 20 per cent suspension. Samples of 0.5 cc of suspension were centrifuged in tubes 9.5 cm in length and 0.9 cm in internal diameter, and the supernatant salt was discarded. To the packed cells were added 0.5 cc samples of serum or plasma. The plasma contained as anticoagulant heparin, in 15 per cent solution in distilled water, in a concentration of 130 mg per one hundred cubic centimeters of whole blood, routinely, serum and erythrocytes were obtained from defibrinated blood. The suspension was acidified by equilibration with mixtures of oxygen and carbon dioxide at room temperature or by the addition to plasma or to serum of 5 per cent (by volume) of certain acids, e. g., 0.85 normal lactic acid or $\frac{1}{3}$ normal hydrochloric acid (see section 6). The suspensions containing acidified serum were then incubated for from one to two hours at 37 C and centrifuged. The percentage increase of hemolysis was estimated by determining the hemoglobin content of the serum or plasma compared with 100 per cent hemolysis produced by distilled water.

(c) *Blood p_H , Blood Gases*—The determinations of the p_H of blood by the glass electrode method¹² and of the carbon dioxide and the oxygen content of blood¹¹ were performed on samples of arterial blood kept at 0 C, containing 130 mg of heparin per hundred cubic centimeters of blood.

(d) *Other Determinations*—The methods of estimation of the formed elements of the blood,¹³ the serum bilirubin,¹⁴ the platelets,¹⁵ the clotting time,¹⁶ the plasma proteins,¹⁷ the Donath-Landsteiner reaction,¹⁸ the resistance of the red blood cells to hypotonic saline solution,¹⁹ the hemosiderin content of the urine and²⁰ the

12 Dill, D. B., Daly, C., and Forbes, W. H. The p_H of Serum and Red Cells, *J. Biol. Chem.* **117** 569, 1937.

13 Wintrobe, M. M. Macroscopic Examination of the Blood, *Am. J. M. Sc.* **185** 58, 1933.

14 Barron, E. S. G. Bilirubinemia, *Medicine* **10**:77, 1931.

15 Pohle, F. J. The Blood Platelet Count in Relation to the Menstrual Cycle in Normal Women, *Am. J. M. Sc.* **197** 40, 1939.

16 Pohle, F. J., and Taylor, F. H. L. The Coagulation Defect in Hemophilia. The Effect in Hemophilia of Intramuscular Administration of a Globulin Substance Derived from Normal Human Plasma, *J. Clin. Investigation* **16** 741, 1937.

17 Ham, T. H., and Curtis, F. C. Plasma Fibrinogen Response in Man. Influence of the Nutritional State, Induced Hyperpyrexia, Infectious Disease and Liver Damage, *Medicine* **17** 413, 1938.

18 MacKenzie, G. M. Paroxysmal Hemoglobinuria, *Medicine* **8** 159, 1929.

19 Daland, G. A., and Worthley, K. The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, *J. Lab. & Clin. Med.* **20** 1122, 1935.

20 Cook, S. F. Structure and Composition of Hemosiderine, *J. Biol. Chem.* **82** 595, 1929.

concentrations of urobilin, urobilinogen²¹ and coproporphyrin²² in the urine and in the stools have been described elsewhere

1 BLOOD PICTURE

The peripheral blood of 5 adult patients with paroxysmal nocturnal hemoglobinuria was characteristic of severe or of moderately severe chronic hemolytic anemia, as was evident from signs both of increased destruction of red blood cells and of active regeneration of blood. The major sign of destruction of blood and a fundamental feature of the disease was the finding of free hemoglobin in the blood plasma of all 5 patients at all times, whether hemoglobin was excreted in the urine or not. Apparently the hemoglobinemia is permanent, as has been stated by Hamburger and Bernstein.⁴ The concentration of hemoglobin in the plasma varied from 11 to 280 mg per hundred cubic centimeters, for the lower concentrations the presence of hemoglobin was not apparent on inspection of the samples but was measurable by the benzidine method and detectable by spectrophotometric examination. In urine free from red cells, oxyhemoglobin was identified by spectrophotometric methods. Quantitatively the amount of hemoglobin excreted in the urine in a twelve hour period varied over an extremely wide range (table 1). Although there was a direct relation between the level of plasma hemoglobin and the amount of hemoglobin appearing in the urine, there was no definite threshold for excretion of this protein. This corresponds with the observations of Ottenberg and Fox²³ for normal subjects receiving intravenous injections of hemoglobin solutions. Hemoglobin was usually absent from the urine when the hemoglobin content of the plasma varied from 15 to 30 mg per hundred cubic centimeters. When the concentration in the plasma was 30 to 100 mg per hundred cubic centimeters the urine usually showed significant amounts of hemoglobin, and when it varied from 100 to 250 mg per hundred cubic centimeters the excretion frequently was extreme, the color of the urine varying from red to black. There were important exceptions to these generalizations, however, in case 4 hemoglobin was always present in the urine in detectable amounts when the level in the plasma was less than 30 mg per hundred cubic centimeters, in case 1, on the contrary, no hemoglobin appeared in the urine for several days at a

21 Watson, C J. Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* **6** 458, 1936.

22 Brugsch, J T, and Keys, A. Quantitative Separation and Estimation of Various Porphyrins in Biological Materials, *Proc Soc Exper Biol & Med* **38** 557, 1938.

23 Ottenberg, R, and Fox, C L. The Rate of Removal of Hemoglobin from the Circulation and Its Renal Threshold in Human Beings, *Am J Physiol* **123** 516, 1938.

time with concentration in the plasma of from 60 to 120 mg per hundred cubic centimeters. Undoubtedly the chronic hemosiderinuria observed in these cases and emphasized by others²⁴ is a direct result of the chronic hemoglobinemia. Although bilirubinemia was present, the degree of jaundice was less than might have been expected from the chronic hemoglobinemia. Similarly, the products of breakdown of hemoglobin were not excreted in amounts comparable to the amount of available free hemoglobin. The concentration of urobilinogen and of porphyrins in the urine and in the stools was normal or only moderately elevated. Decreased renal function was observed in the 3 cases in which examination was made and uremia occurred in case 3.

The accelerated production of red blood cells was evidenced by chronic reticulocytosis, the average percentage of reticulocytes in each of the 5 cases being between 10 and 28. The red blood cells varied from a normal to a moderately macrocytic mean corpuscular volume, as is found in other hemolytic anemias. In 3 patients (cases 1, 2 and 3) whose spleens had not been removed there were moderate leukopenia and thrombocytopenia, as observed by others²⁵. Moderate splenomegaly was present in 2 of these patients (cases 2 and 3). In 2 patients, (cases 4 and 5) whose spleens had been removed several years prior to these observations the leukocyte counts and the platelet levels were normal. For all 5 patients the osmotic fragility of the red blood cells to hypotonic saline solutions was normal whether samples of blood were obtained during a severe or a mild hemolytic phase. Serologic tests for syphilis gave negative results, and the Donath-Landsteiner reaction was negative in the 4 cases in which the test was made. A summary of the blood chemistry and other laboratory observations is presented in table 1, and a brief review of each case is given in the appendix.

2 RELATION OF HEMOGLOBINEMIA TO SLEEP

Quantitative estimations of the concentration of hemoglobin in the plasma and urine were made for periods varying from three to six days on specimens obtained every three hours day and night or on specimens obtained at longer intervals. In cases 1 and 2, in which the spleens had not been removed, an increase in hemoglobinemia was always observed during sleep as compared to the level during waking hours; nocturnal hemoglobinuria was frequently present. A typical example of urinary excretion of hemoglobin during a hemolytic phase of moderate severity (case 1) is illustrated in chart 1. Since hemoglobinuria was an inconstant finding and did not necessarily indicate the variations in hemoglobinemia, the level of the plasma hemoglobin was studied quantitatively as related to sleep.

24 Marchiafava¹ Michel² Witts³ Hamburger and Bernstein⁴

25 Witts³ Hamburger and Bernstein⁴

TABLE 1—Summary of Laboratory Observations on Five Patients with Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria

Case Number	1	2	3	4	5
Sex	M	F	M	M	F
Age	17	39	18	35	30
Duration of disease (estimated to December 1938), years	3	1½	5½#	6½	7
Period of observation	5 months	6 days	15 months	2 months	2 days*
Splenectomy	0	0	0	1935	1937
1 Plasma hemoglobin, mg per 100 cc					
Average	78	37	36	72	104
Range	29-232	4-87	Trace-195	27-270	
Number of determinations	136	13	167	78	1
2 Total excretion of hemoglobin in urine, mg					
Awake, 12 hours					
Average	30†	0	310	850	After sleep
Range	0-208		0-3300	30-2,000	2 specimens
Asleep, 12 hours					dark red,
Average	650	140	520	840	1+ benzidine
Range	160-1700	0-380	0-3100	30-3000	reaction
Number of determinations	9	4	206	60	
3 Red blood cells and hemoglobin					
Red blood cells, millions per cu mm					
Average	1.90	1.80	2.50	2.70	2.50
Range	1.70-2.60	1.70-1.90	1.44-3.50	1.70-3.60	1.90-3.80
Number of determinations	50	2	121	21	11
Hemoglobin, percentage					
Average	42	44	45	53	49
Range	27-55	42-46	20-60	38-71	40-74
Number of determinations	50	2	121	21	10
Reticulocytes, percentage					
Average	23	11	10	10	14
Range	13-47	6-17	0-23	0-24	3-20
Number of determinations	116	6	207	69	5
Hematocrit, percentage (average)	23	24	23	26	22
Mean corpuscular volume, cubic microns (average)	119	131	89	97	118
Mean corpuscular hemoglobin concentration (average)	29	29	30	31	29
Mean corpuscular diameter, microns	8.2	8.5	7.8	8.7	8.7
Standard deviation from mean diameter, microns	0.92	0.76	0.71	0.93	0.81
Coefficient of variation of diameters, percentage	11.2	9.9	9.0	11.0	9.2

It was observed that increased hemoglobinemia was associated with sleep either at night or during the day (chart 2) The increase in hemoglobinemia did not occur if the patient was kept awake for twenty-seven hours, but it was noted when the patient slept during the day.

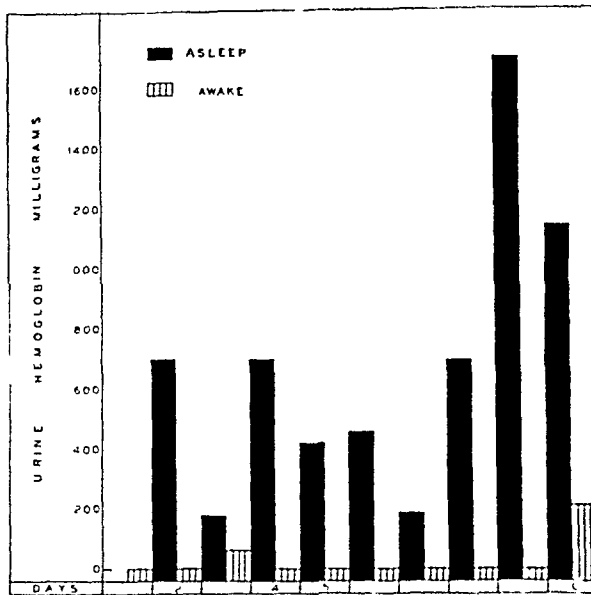


Chart 1 (case 1) —Relation of hemoglobinuria to sleep Excretion of hemoglobin in the urine of a patient with paroxysmal nocturnal hemoglobinuria The daily output was divided into two periods of twelve hours, a period of sleep (from 9 p m through 9 a m) and a period of waking (from 9 a m through 9 p m). The patient slept from 9 p m through 6 a m

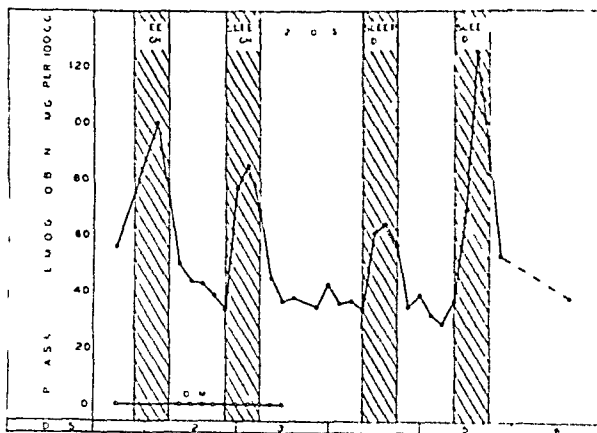


Chart 2 (case 1) —Chart showing that increased hemoglobinemia is related to sleep The rise in hemoglobin content of the plasma was absent during twenty-seven hours without sleep and was reversed by sleep during the day

To control the effect of posture and of ingestion of nourishment, the patient, case 1, was fed identical samples of food and fluids every three hours for forty-five hours (chart 3) For twelve hours he was kept awake at complete rest in bed in the positions assumed during sleep,

in the subsequent nine hours he was permitted to sleep except during feedings and venipunctures. It was evident that the increase in hemoglobinemia was correlated with sleep and not with posture, with ingestion of food or fluid, or with the time of day or night during which sleep occurred. However, in case 4, in which the spleen had been removed, there was no increase in hemoglobinemia or hemoglobinuria during sleep, although before splenectomy definite nocturnal hemoglobinuria had been observed by Hamburger and Bernstein⁴. The excretion of hemoglobin in the urine in case 4 for an eleven day period during a moderately severe hemolytic phase is illustrated in chart 4. In case 5, in which splenectomy also had been done, there was no opportunity to study the excretion of hemoglobin as related to sleep.

3 RELATION OF HEMOLYSIS IN VIVO TO ACID-BASE EQUILIBRIUM

Sleep is known to be associated with decreased pulmonary ventilation, with slight elevation of the carbon dioxide content of the arterial blood

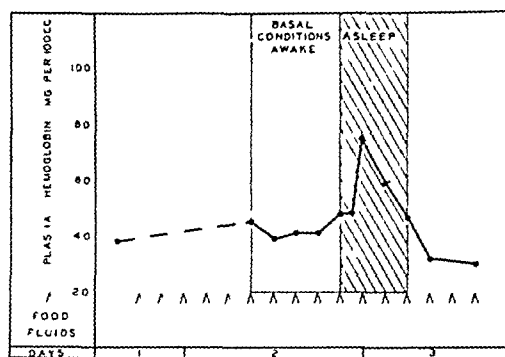


Chart 3 (case 1)—Chart showing that increased hemoglobinemia is related to sleep and not to posture or to ingestion of food and fluids. The patient received the same amount of food and fluids every three hours for forty-five hours. For twelve hours he was kept awake at complete rest in bed in the positions assumed during sleep. For nine hours he was allowed to sleep.

and with a consequent decrease in p_H , as observed by Hastings²⁶ and by Kleitman²⁷. For this reason it was suspected that elevation of the hemoglobin content of the plasma during sleep was associated with variation in the acid-base equilibrium of the blood. To investigate this possibility, 2 patients were treated with acid and with basic salts, 1 was subjected to hyperventilation during sleep, and the p_H of the arterial blood and the carbon dioxide tension of a third patient were observed during sleep and during waking hours. Because of anemia none of the 5 patients was subjected to severe muscular exercise as a method of producing increased acidity of the blood.

²⁶ Hastings, A. B. Personal communication to the author.

²⁷ Kleitman, N. Sleep, *Physiol Rev* 9:624, 1929.

The oral administration of ammonium chloride in case 1 (10 Gm daily for two days followed by 5 Gm daily for six days) was associated with an increase in hemoglobinuria during sleep for the first two days of treatment. For the subsequent six days of acid therapy and for a sixteen day period in which no acid treatment was given the urine contained only a trace of hemoglobin on three occasions. In case 4 the oral administration on two separate occasions of 57 Gm and 127 Gm respectively of ammonium chloride during twenty-four hours was accompanied by increase of hemoglobin in the plasma and in the urine and by decrease in the p_H of the arterial blood in the second instance from 7.33 to 7.23. In case 3, in which the patient had pyelonephritis, the administration of 4 Gm of ammonium chloride and 12 Gm of ammonium mandelate daily for six days did not produce an increase in hemoglobinemia or hemoglobinuria.

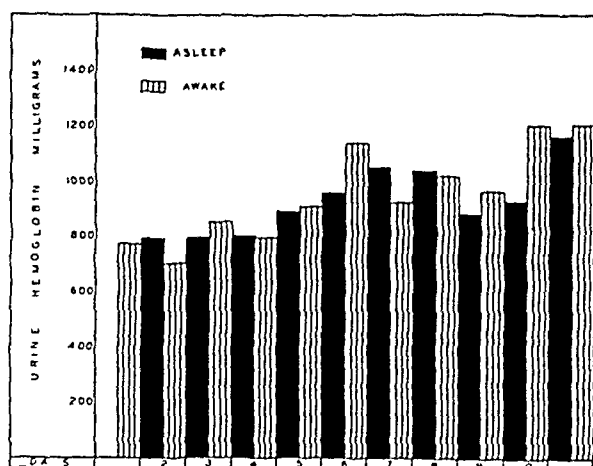


Chart 4 (case 4) —The chart shows the excretion of hemoglobin in the urine after splenectomy. No increase in hemoglobinuria was associated with sleep.

Sodium bicarbonate administered orally in the large dose of 65 Gm in twenty-four hours produced a transient decrease in the hemoglobin content of the plasma and of the urine in cases 1 and 4. As is shown in chart 5, there was no significant rise in the value for plasma hemoglobin during sleep for the first night after ingestion of alkali, the carbon dioxide-combining power increased significantly with this therapy. For sixteen days the patient in case 1 received daily large doses of alkaline salts (40 Gm of sodium bicarbonate for thirteen days and 56 Gm of sodium citrate for three days). There was no excretion of hemoglobin for eight days, but in the subsequent period the nocturnal hemoglobinuria returned and increased materially, being associated with increase in the level of hemoglobin in the plasma. Administration of 45 Gm of sodium bicarbonate during the sleeping hours without alkali during the day

produced a decrease in nocturnal hemoglobinuria but a large excretion of hemoglobin during waking hours. Complete and sudden withdrawal of alkali therapy, in contrast to discontinuing acid salts, produced extreme hemoglobinemia and hemoglobinuria in cases 1 and 4. In case 1 the concentrations of hemoglobin in the plasma reached levels of from 230 to 280 mg per hundred cubic centimeters and the urine was red to black day and night. It was necessary to administer decreasing amounts of alkali over a period of six weeks to reduce in part the hemolytic activity. Because of the untoward effect of both the acid and the alkali salts in the amounts given, they were considered unsatisfactory for therapeutic administration.

The respiratory rate and depth during sleep were controlled artificially in case 1 by a Drinker respirator. During the first observations the rate of respiration and the volume of an exchange were adjusted to coincide with the spontaneous respiration of the patient. The usual rise in hemoglobin content of the plasma and of the urine was observed during natural sleep in the machine, and there was no significant alteration of alkali reserve as measured on samples of venous blood taken before and during sleep. Hyperventilation during a subsequent night was produced during six hours of natural sleep by increasing significantly the rate of respiration and the volume of air exchange. As is evident from the data in table 2, this hyperventilation produced significant alkalosis and was accompanied by no increase in hemoglobinemia or hemoglobinuria. However, during the same twenty-four hour period, natural sleep, without hyperventilation was associated with a more acid but normal p_H of the arterial blood and with a significant increase in hemoglobinemia and hemoglobinuria.

No significant alteration of p_H was demonstrable on samples of arterial blood obtained from the patient in case 2 during waking and sleeping hours (table 3). However, an increase of hemoglobin in both plasma and urine was associated with sleep.

4. RELATION OF HEMOLYSIS IN VITRO TO ACID-BASE EQUILIBRIUM

It was noted that on standing for four hours at room temperature or in the incubator at 37.5 C. samples of whole clotted blood (case 1), samples of defibrinated blood and samples of whole blood containing heparin as an anticoagulant all showed progressive hemolysis, with approximately 2 per cent destruction of red blood cells in the four hours. Comparable samples of blood from normal subjects showed no hemolysis. At ice box temperature there was minimal hemolysis of samples of the patient's blood. From these observations a change in p_H was suspected to be related to the increased hemolysis of samples standing at room temperature or incubator temperature. Accordingly,

TABLE 2—*Effect of Alkalosis on Hemoglobinemia*

Condition	Plasma Hemoglobin, Mg /100 Cc	Urine Hemoglobin	Alkali Reserve (Total CO ₂ at p CO ₂ of 40 mm mercury) Vol per Cent		Arterial CO ₂ Con- tent, Vol per Cent	Arterial Partial Pressure CO ₂ Mm of Mercury	pH	Oxygen Capac- ity, Vol per Cent	Oxygen Satura- tion, Percentage	Type of Blood
Awake and ambulatory	95.150	++ to +++	16.8					7.15		Venous
Natural sleep, respiration normal	230	+++	13.5		11.1	12.0	7.3	8.65	93.9	Arterial
Natural sleep, hyperventilation	110.150	+++	17.2		12.6	28.0	7.47	8.31	97.95	Arterial

* Alkalosis was produced during natural sleep by hyperventilation

the influence of variation in p_H on hemolysis of samples of blood from each of the 5 patients was investigated with a variety of acids

(a) *Carbon Dioxide*—Equilibration of defibrinated blood from the patient or of his whole blood containing heparin with mixtures of oxygen and carbon dioxide produced hemolysis roughly proportional to the

TABLE 3 (Case 2) —*Plasma Hemoglobin and p_H of the Blood During Sleep**

Status of Patient	Plasma Hemoglobin, Mg /100 Cc	Arterial CO ₂ Content, Vol per Cent	Arterial Partial Pressure CO ₂ , Mm of Mercury	p_H	Oxygen Capacity, Vol per Cent	Oxygen Saturation, Percentage
Awake and ambulatory (noon)	40	52.3	44.9	7.35	10.46	88.6
Asleep (midnight)	85	50.4	43.9	7.35	9.49	98
Awake and ambulatory (9 a m)	60	50.7	41.4	7.38	10.61	91

* Samples of arterial blood were taken during periods of both sleep and waking. Note that there was an increase of the hemoglobin content of the plasma during sleep but no significant change in p_H .

TABLE 4—*Influence of Carbon Dioxide on the Degree of Hemolysis*

A. Samples of blood from the patient in case 1 and from a normal subject. Whole blood containing heparin as anticoagulant was equilibrated for 10 minutes at room temperature with the continuous flow of 2 liter samples of each gas mixture.

Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage	Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage
Air, 100	0	0	CO ₂ , 5 O ₂ , 95	4	0
CO ₂ , 2.5 O ₂ , 97.5	1	0	CO ₂ , 10 O ₂ , 90	4	0

B. Samples of blood from the patient in case 3 and from a normal subject. Whole defibrinated blood was washed with 2 liter samples of each gas mixture at room temperature for 20 minutes and equilibrated for an additional 10 minutes.

Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage	Gas Mixture, Percentage	Hemolysis of Patient's Blood, Percentage	Hemolysis of Normal Blood, Percentage
O ₂ , 100	0	0	CO ₂ , 10 O ₂ , 90	7	0
N ₂ , 100	0	0	CO ₂ , 10 N ₂ , 90	7	0

carbon dioxide tension when the partial pressure of carbon dioxide ranged from 4 to 40 mm of mercury. This effect was related to the presence of carbon dioxide and not to the degree of oxygen saturation, since equilibration with oxygen, air or nitrogen alone caused no hemolysis and since the substitution of nitrogen for oxygen in the carbon dioxide mixtures caused no significant change in the degree of hemolysis (table 4). There was no hemolysis of normal red blood cells by the

aforementioned procedures when suspended in normal serum or in serum from the patient

(b) *Lactic Acid and Sodium Bicarbonate*—The addition to serum or to plasma (heparin) of lactic acid in a 10 or 20 millimolar concentration caused partial hemolysis of a 20 per cent suspension of washed red blood cells from the patient in fifteen minutes at room temperature. Hemolysis was further increased by subsequent equilibration of the suspension with carbon dioxide. The addition of sodium bicarbonate in a 10 or 20 millimolar concentration caused striking decrease in the hemolytic action of carbon dioxide. The addition of sodium chloride in the same concentrations did not inhibit hemolysis. The data from one experiment are shown in table 5. Therefore, the degree of hemolysis was apparently related to change in p_H . There was no hemolysis of

TABLE 5—*Influence on Hemolysis by Carbon Dioxide of Lactic Acid and of Sodium Bicarbonate Added to Serum**

	Hemolysis of Patient's Blood		Hemolysis of Normal Blood	
	Standing 30 Minutes at Room Temperature (No CO ₂) Percentage	Equilibrated with 10 per Cent CO ₂ and 90 per Cent O ₂ for 10 Minutes at Room Temperature Percentage	Standing 30 Minutes at Room Temperature (No CO ₂) Percentage	Equilibrated with 10 per Cent CO ₂ and 90 per Cent O ₂ for 10 Minutes at Room Temperature Percentage
Lactic acid	3	9	±	±
Unaltered serum	±	1	±	±
Sodium bicarbonate	0	0.6	±	±

* The samples of blood were taken from the patient in case 2 and from a normal subject. Washed packed red blood cells were used in 20 per cent suspension. Acid or alkaline solution was added to serum in a final concentration of 20 millimols and 5 per cent dilution of serum.

normal red blood cells in similar mixtures containing normal serum or serum from the patient.

(c) *Influence of p_H on Hemolysis*—Further observations of the influence on hemolysis of the hydrogen ion concentration were made on samples of blood in cases 3 and 5, a variety of acids being employed and the effect being investigated of acidified serum from the patients and from normal subjects with blood of the same group on the washed red blood cells both of the patients and of normal subjects. For each acid a series of solutions containing a constant concentration of acid and varying amounts of sodium hydroxide was made, so that the addition of 5 per cent (by volume) of the mixture to serum produced a range of p_H of approximately 6 to 8. The first solution of each series contained no alkali. The only two variables, therefore, were the p_H and the salt concentration. The hydrogen ion concentrations of the mixture of serum and acid-alkali were estimated with rough accuracy

by the quinhydrone method²⁸ The results of typical experiments are shown in chart 6 and table 6

When the washed red blood cells from the patient in case 3 were suspended in serum from the patient or from normal subjects, hemolysis increased with increasing acidity for lactic, hydrochloric, nitric, acetic and sulfuric acids Hemolysis was absent with citric acid and was

TABLE 6—*Influence on Hemolysis of Certain Acids and Acid-Sodium Hydroxide Mixtures Added to Serum**

A Serum from Patient in Case 3				
Composition of Acid NaOH Mixtures (Diluted to 100 Cc)	4.5 N NaOH Volume Added Cc	pH Resulting from Adding 0.05 Cc of Acid NaOH Mixture to 0.95 Cc Serum	Hemolysis of Red Blood Cells (Case 3) Percentage	Hemolysis of Red Blood Cells from (Normal Subject) Percentage
Control (unaltered serum)		7.7	1	0
50 cc	0	6.0	11	0
0.54 normal nitric acid	2	6.2	15	0
	8	7.6	0	0
	10	8.0	0	0
50 cc	0	6.3	15	0
0.48 normal acetic acid	2	6.7	9	0
	8	7.8	0	0
	10	7.9	0	0
50 cc	0	6.2	5	0
0.48 normal oxalic acid	2	6.5	3	0
	8	7.6	0	0
	10	8.0	0	0
50 cc	0	6.2	3	0
0.40 normal orthophosphoric acid	2	6.6	3	0
	8	7.3	0	0
	10	7.6	0	0
B Serum from Normal Subject				
Control (unaltered serum)		7.7	0	0
50 cc	0	6.5 [†]	8	0
0.90 normal hydrochloric acid	2	6.8	7	0
	8	7.8	0	0
	10	8.2	0	0
50 cc	0	6.5	7	0
0.50 normal sulfuric acid	2	6.8	1	0
	8	7.8	0	0
	10	8.2	0	0

* A 5 per cent suspension in serum of washed packed red blood cells from the patient in case 3 and from a normal subject of the same blood group were incubated for one hour at 37.5 C

† Normality titrated with tenth normal sodium hydroxide with the use of Tashiro's indicator

diminished with oxalic and phosphoric acids in the concentrations employed The degree of hemolysis varied somewhat with the serum used, whether from the patient or from a normal subject No significant hemolysis occurred, however, when normal red blood cells were suspended in the acidified serums The apparent inhibitory effect on hemolysis of citric acid of certain salts will be discussed later (section 8d)

28 Hawk, P. B., and Bergheim, O. Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1937

and in a second communication^{9a} dealing with the complement activity of serum. It should be emphasized that hemolysis of the erythrocytes was frequently observed without the addition of acid and that hemolysis was always present and materially increased by the addition of certain acids and was decreased or eliminated by the addition of alkali. However, hemolysis was not caused by the effect of acid alone, as will be shown.

5 FUNDAMENTAL ABNORMALITY OF RED BLOOD CELLS

Although the p_H of plasma or serum influences the degree of hemolysis, a more important observation is the demonstration that the fundamental abnormality for this disease resides in the red blood cells and not in the serum. It has been shown that the washed red blood cells from these 5 patients were always hemolyzed in the acidified plasma

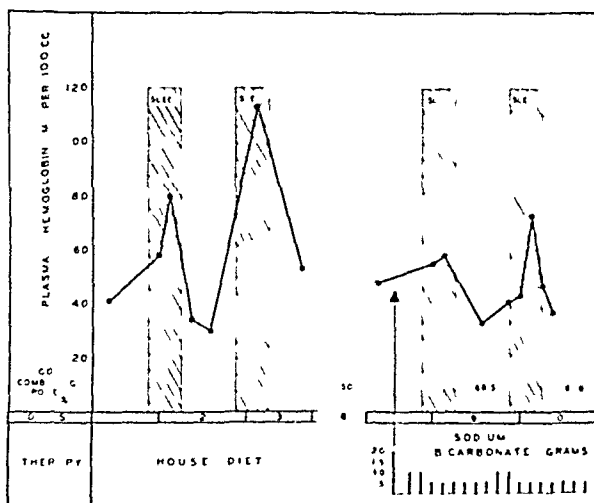


Chart 5 (case 1) —Influence of ingestion of alkaline salt on hemoglobinemia. The chart shows the concentrations of plasma hemoglobin during a period without therapy and after oral administration of large doses of sodium bicarbonate.

(heparin) or serum of the same blood group of all normal subjects tested. On the other hand, the washed red blood cells from normal subjects were never hemolyzed by the acidified plasma or serum of the 5 patients tested. Since the blood of the patients in cases 1, 2 and 4 was of group IV-O, it was possible to test their red cells with the serum of normal subjects with blood of all four groups. Since the blood of the patients in cases 3 and 5 was of group I-AB, it was possible to demonstrate the lack of hemolytic activity of their serums for the red cells from blood of all four groups from normal subjects. The erythrocytes and serums of 30 normal persons were employed in these observations. Accordingly, there was no apparent association of the four blood groups in this hemolytic system. The M and N blood groups were not tested.

(a) Difference in Susceptibility of Red Blood Cells to Hemolysis—

A difference in susceptibility of washed erythrocytes to hemolysis was demonstrated in cases 1 and 4 as well as in cases 3 and 5. Since the blood groups were the same for each pair of these 4 cases, it was possible to suspend washed erythrocytes from 2 patients in samples of the same serum and compare the degree of hemolysis. The data for one observation are shown in table 7. In both instances the erythrocytes showing the greater susceptibility to hemolysis were obtained from the patients in cases 1 and 5, who were in a moderately severe hemolytic phase, as evidenced by high concentrations of hemoglobinemia and hemoglobinuria. The other 2 patients, on the contrary, showed hemoglobinemia and hemoglobinuria which was moderate (case 3) or slight (case 4). There was definite evidence, therefore, first, of a difference

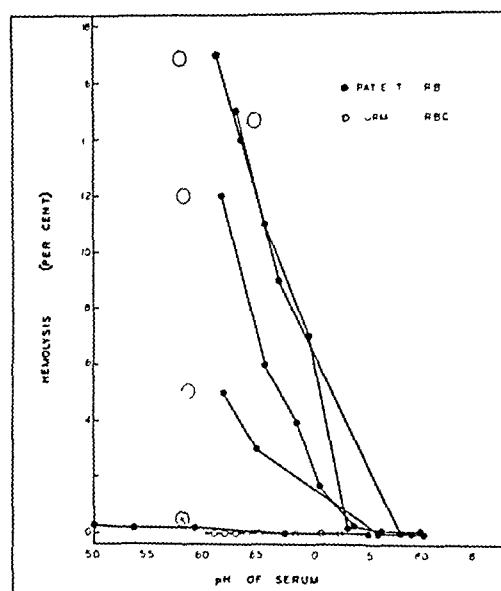


Chart 6 (case 3)—Influence on hemolysis of certain acids. The chart indicates hemolysis of erythrocytes from the patient in case 3 compared with the lack of hemolysis of normal erythrocytes, when suspended in serum from the same patient, acidified by the addition of a constant concentration of any one of the following acids, mixed with varying amounts of sodium hydroxide: (1) hydrochloric, (2) acetic, (3) lactic, (4) oxalic and (5) citric. The concentration of acid in serum for lactic and citric acids was 35 and 18 millimols, respectively. (For other acids see table 6.)

in susceptibility to hemolysis for erythrocytes from different patients and, second, of a correlation between hemolytic susceptibility of the erythrocytes *in vitro* and the clinical severity of the hemolytic process.

*(b) Effect of Erythrocyte Concentration on Hemolysis—*The percentage of hemolysis of washed red blood cells varied inversely as the concentration of cells, as is evident from the curves in chart 7. Complete hemolysis was never observed under the conditions employed in this study. The usual range was from 2 to 30 per cent.

(c) *Effect of One Hemolytic Reaction on Susceptibility of Erythrocytes to Further Hemolysis*—Washed red blood cells from the patient in case 1 were equilibrated with 10 per cent carbon dioxide and 90 per cent oxygen. After the first equilibration the cells were washed three times in saline solution and suspended at the same concentration in fresh serum for a second equilibration. The percentage of hemolysis was approximately the same for both equilibrations. There was no significant difference in the percentage of hemolysis between erythrocytes washed three times and those washed six times in saline solution. It was apparent, therefore, that the hemolytic susceptibility was not altered by multiple washings of the erythrocytes and also that erythrocytes susceptible to hemolysis still remained after one hemolytic reaction had occurred.

TABLE 7—*Difference in Susceptibility to Hemolysis of Erythrocytes from Patients in Cases 3 and 5**

Source of Red Blood Cells	Source of Serum	Hemolysis After Incubation for One Hour at 37.5 C	
		Without Acid, Percentage	0.05 Cc 1/3 Normal HCl Added to 0.95 Cc Serum, Percentage
Normal subject	Normal subject	0	0
	Patient (case 3)	0	0
Patient (case 3)	Normal subject	0	10
	Patient (case 3)	0	13
Patient (case 5)	Normal subject	5	15
	Patient (case 3)	8	16

* A 5 per cent suspension of washed packed red blood cells was used. All samples were of blood group I AB.

6 FRESH HUMAN PLASMA OR SERUM REQUIRED FOR HEMOLYSIS

Hemolysis of the abnormal erythrocytes in all 5 cases occurred only in fresh human plasma (heparin) or serum. Hemolysis did not occur in physiologic solution of sodium chloride or in plasma or serum which had been heated for thirty minutes at 50 or at 56 C. Therefore, a factor present in human plasma (heparin) and serum was essential for hemolysis of the abnormal red blood cells. The relation of this factor to the complement activity of human serum will be discussed in detail in another communication.^{2a}

(a) *Effect of Exposing Serum to Various Temperatures for Thirty Minutes*—Serums exposed to a temperature of 50 or 56 C for thirty minutes showed no hemolytic activity for the washed red blood cells of any of the 5 patients. There was no striking difference in the activity of serums exposed for thirty minutes at temperatures of from 0 to 40 C.

(b) *Effect of Dilution of Serum*—The hemolytic activity of serums was decreased by dilution with saline solution or with serum heated at 56 C for thirty minutes. Hemolysis was seldom demonstrable in dilution beyond 1 to 3 or 1 to 4. In some instances the hemolytic activity of serum was not demonstrable in a 1 to 2 dilution.

(c) *Failure of Guinea Pig Complement to Reactivate Heated Serum*—The hemolytic activity was not restored to serum heated at 56 C for thirty minutes by the addition of sufficient guinea pig serum to reestablish or increase the original complement concentration of the serum as measured by sensitized red blood cells. This will be discussed in another communication.^{9a}

(d) *Inhibition of Hemolysis by Certain Salts*—The hemolytic activity of carbon dioxide was prevented by the addition to whole blood,

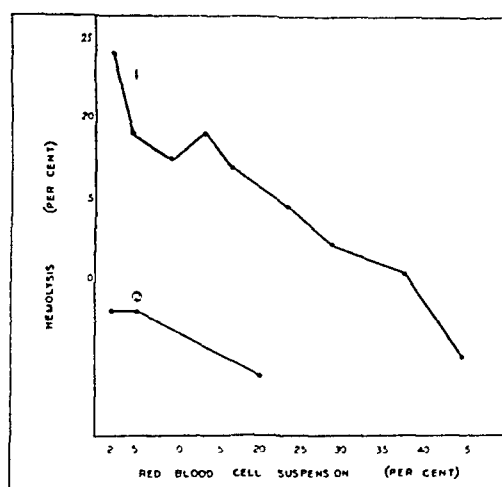


Chart 7 (case 3) —Effect of erythrocyte concentration on hemolysis. Curve 1 indicates washed packed red blood cells from the patient suspended at varying concentrations in samples of a pooled specimen of serum from the same patient containing lactic acid (20 millimols). The suspensions were incubated for two hours at 37.5 C. Curve 2 indicates washed packed red blood cells from the patient in case 1 in serum from the same patient. The suspensions were equilibrated at room temperature for ten minutes with 10 per cent carbon dioxide and 90 per cent oxygen.

to plasma (heparin) or to serum of sodium citrate (0.3 per cent) potassium oxalate (0.2 per cent) or potassium cyanide (0.13 per cent). One tenth of the aforementioned concentration of potassium cyanide (0.01 per cent), however, did not inhibit hemolysis. The hemolytic activity of serum treated with 0.13 per cent potassium cyanide or of serum heated at 56 C for thirty minutes was not restored by the addition of a 0.4 per cent solution of methylene blue in a concentration of 0.01 or 0.1 Gm per hundred cubic centimeters. Susceptibility of the erythrocytes to hemolysis was not altered by exposure to these salts. Washed red blood cells obtained from samples of whole blood containing the aforemen-

tioned salts showed the same hemolytic reactions as did untreated cells when resuspended in fresh serum. The inhibitory effect of these salts, therefore, apparently was on the serum factor or on the interaction between the serum factor and the red blood cell.

7 DONATH-LANDSTEINER REACTION CHILLING OF BODY

The manifestations of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria are contrasted (table 8) with the manifestations of paroxysmal hemoglobinuria from chilling. In the nocturnal type of disease the Donath-Landsteiner reaction is negative and chilling of the body does not produce a paroxysm of intravascular hemolysis. However, the observation that the patient's red blood cells are frequently hemolyzed to some extent in his own serum during incubation might falsely suggest a positive Donath-Landsteiner reaction. In contrast to the Donath-Landsteiner phenomenon, the patient's serum does not hemolyze normal cells, and previous chilling is not necessary for hemolysis. Further clarification may be made by the hemolysis test with acidified serum. A paroxysm of hemoglobinuria is not induced in the nocturnal type of disease by exposure to cold, yet the presence of variable degrees of hemoglobinemia or the frequent occurrence of hemoglobinuria has caused this disease to be mistaken for paroxysmal hemoglobinuria *é frigore*.

COMMENT

It is apparent that the fundamental abnormality underlying the hemolytic mechanism in the disease chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria resides in the red blood cells. A thermolabile factor essential for hemolysis was found in the patients' plasma and serum and also in the plasma and serum of normal subjects. The patients' serum, however, exhibited no hemolytic action on normal red blood cells. Increase of acidity of plasma or serum within or beyond the physiologic range always produced an increase in the degree of hemolysis, decrease of acidity diminished or eliminated hemolysis. Accordingly, this disease may be distinguished *in vitro* from other hemolytic anemias by a hemolysis test with acidified serum (tables 9 and 10). This test has shown no hemolysis with samples of blood from patients with hemolytic jaundice, hemolytic anemia with sulfamidamide poisoning, acute hemolytic anemia of Lederer, sickle cell anemia, Cooley's anemia, paroxysmal hemoglobinuria with chilling (carbon dioxide equilibration by van den Bergh⁶ and Jordan⁹), pernicious anemia, hypochromic anemia and alcoholic cirrhosis of the liver with anemia.

Two simplified methods of performing the hemolysis test with acidified serum are as follows. Blood defibrinated with glass beads is

TABLE 8—Comparison of Certain Features of Paroxysmal Nocturnal Hemoglobinuria and Hemoglobinuria from Chilling

Feature of Disease	Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria (Marchiafava Michel Disease)	Paroxysmal Hemoglobinuria from Chilling (Donath Landsteiner)
1 Fundamental abnormality	In the red blood cells	In the serum (hemolytic antibody)
2 Donath Landsteiner reaction	Negative	Positive (hemolytic antibody fixed to red cells only in cold)
3 Hemolysis by patient's serum of normal red blood cells of same blood group	None	All red blood cells hemolyzed by antibody in Donath Landsteiner reaction
4 Complement required for in vitro hemolysis	Fresh human serum, required for hemolysis, complement or complement like substance,* not patient's cells frequently hemolyzed by any serum, normal cells not hemolyzed by patient's serum	Complement required, supplied by human serum or by guinea pig serum
5 Hemolysis on incubation alone, serum and red blood cells at 37.5 C	Patient's cells hemolyzed significantly by fresh human serum, normal cells not hemolyzed by patient's serum, same blood groups employed	None
6 Hemolysis test with acidified serum, pH adjusted to approximately 6.5 with lactic acid, hydrochloric acid or equilibration with CO ₂ O ₂ mix 37.5 C for one hour	Chronic, usually increased during sleep	No hemolysis of patient's cells in patient's serum exposed to CO ₂ at 37 C (Van den Bergh ⁶ and Jordan ⁹)
7 Hemoglobinemia	Frequent, usually greater during sleep (paroxysmal nocturnal hemoglobinuria)	Absent except during reaction following chilling of the body
8 Hemoglobinuria	Does not produce hemolytic episode	Absent except during reaction following chilling of body (paroxysmal hemoglobinuria v. frigore)
9 Chilling of body	Absent	Produces paroxysm of intravascular hemolysis with hemoglobinemia and hemoglobinuria
10 Syphilis	Chronic hemolytic anemia	Usually present
11 Anemia		Acute anemia following paroxysm, no anemia between attacks

* To be discussed in another communication¹¹

employed, since anticoagulants other than heparin inhibit the hemolysis completely. In the first method, 5 cc of defibrinated whole blood is equilibrated in an ordinary tonometer for fifteen minutes at room temperature with a gas mixture containing 10 per cent carbon dioxide and 90 per cent oxygen (table 4). The suspension is then centrifuged. Blood from a patient with paroxysmal nocturnal hemoglobinuria shows from 5 to 30 per cent hemolysis after such equilibration, whereas blood from a normal subject should show no hemolysis or only a trace. In the second method, 10 cc of defibrinated blood is centrifuged for removal of serum, the erythrocytes are made to a 5 per cent suspension in salt solution, and two samples of 1 cc each are measured into small tubes and the salt removed after centrifugation. The packed erythrocytes of one tube are suspended in 1 cc of unaltered serum, those of the other tube are suspended in a mixture containing 0.95 cc of serum and 0.05 cc of $\frac{1}{3}$ normal hydrochloric acid (p_H , approximately 6.5), these are incubated for 1 hour at 37 C and centrifuged. In paroxysmal nocturnal hemoglobinuria the tube containing unaltered serum may show no hemolysis or lysis of from 1 to 10 per cent, the tube containing acidified serum will show a greater degree of hemolysis, varying from 2 to 30 per cent. There should be no significant hemolysis in either tube for blood samples from normal subjects or from persons with other diseases. If the test gives a positive result, suitable controls may be set up as outlined in tables 7, 9 and 10.

Van den Bergh,⁹ in 1911, reported observations *in vitro* similar in part to those just described in the case of a patient with hemolytic anemia associated with the crises of hemoglobinuria (undoubtedly the syndrome later identified by Marchiafava and Micheli). Van den Bergh found that the patient's red blood cells were hemolyzed at 37 C in an atmosphere containing carbon dioxide when suspended in the serums from the patient and from 2 normal subjects, the blood groups were not mentioned. The patient's serum did not hemolyze normal cells. He also observed that heating serum for thirty minutes at 50 C destroyed the hemolytic activity of the serum and that hemolysis was not restored by adding small amounts of fresh human or guinea pig serum. The author concluded that the hemolysis was caused not by specific hemolytic substances in the serum but by an abnormal "fragility" of the erythrocytes to carbon dioxide which did not manifest itself in contact with dilute solutions of sodium chloride. However, as was shown by van den Bergh in this case and by all subsequent investigators, the resistance of red blood cells to hypotonic salt solutions is normal. This disease, therefore, is unrelated to acquired or to congenital hemolytic jaundice characterized by abnormally increased osmotic fragility of the erythrocytes to hypotonic solutions.

TABLE 9—*Donath-Landsteiner Reaction Compared to Result of Hemolysis Test with Acidified Serum*

Source of Serum	Treatment of Serum	Source of Red Blood Cells	Treatment of Suspension of Red Blood Cells (15%) in Serum	Color of Supernatant Serum	Hemoglobin Concentration of Supernatant Serum, Mg/100 Cc	Hemolysis,† Percentage	Comment
Patient (case 3) Control	Unaltered	No Cells Added	No Cells Added	Light brown Straw	60 15		Hemoglobin present in serum before use
Patient (case 3)	Unaltered	Patient (case 3) Control	Chilled to 1 C for 30 minutes, incubated at 37.5 C for 2 hours	Pink Straw	85 70	0.5* 0.2	Donath Landsteiner reaction without added complement
Patient (case 3)	Unaltered	Patient (case 3) Control	Incubated at 37.5 C for 2 hours	Pink Straw	100 60	0.8* 0.2	Incubation without chilling
Patient (case 3)	Serum acidified with lactic acid (20 milligrams)	Patient (case 3) Control	Incubated at 37.5 C for 2 hours	Dark red Straw	510 60	8 0.2	Hemolysis test with acidified serum
Control		Patient (case 3) Control		Dark red Straw	575 20	10 ±	

* Hemolysis has been observed as high as 10 per cent in other cases after incubation

† Note that the patient's cells were the only red blood cells to be hemolyzed chilling did not increase the hemolysis, a normal serum gave the same hemolytic reactions as the patient's serum, acidified serum produced significant hemolysis only of the patient's red blood cells

The hemolytic system in nocturnal hemoglobinuria differs distinctly from that of paroxysmal hemoglobinuria from cold. In the latter disease the red blood cells are normal, the serum contains a true hemolytic antibody absorbed in the cold by erythrocytes, and after chilling hemolysis occurs in the presence of complement on incubation at 37 C (Donath-Landsteiner reaction). The mechanism of hemolysis in hemoglobinuria from exertion (*Marschhemoglobinurie*) is not understood (Witts,³ Hamburger⁴).

The in vivo observations in cases of paroxysmal nocturnal hemoglobinuria have demonstrated the presence of free hemoglobin in the plasma at all times, indicating continued intravascular hemolysis. The administration of acid-forming salts produced a significant increase in acidity of arterial blood and a transient increase in hemoglobinemia and hemoglobinuria in 2 cases in which there were no complications but failed to do so in 1 case in which acute pyelonephritis was an associated condition. Conversely, a decrease in acidity of the blood, produced by the administration of alkaline salts and by alkalosis from hyperventilation, was associated with transient decrease in intravascular hemolysis. These observations were made on 2 patients, 1 with the spleen intact and the other with spleen removed.

The nocturnal increase in hemoglobinemia was shown to be associated with sleep and not with the patient's posture, with ingestion of food and fluid or with the time of day or night during which sleep occurred. No rise in the hemoglobin content of the plasma occurred during twenty-seven waking hours. It is probable that the increased intravascular hemolysis which occurs during sleep is associated with the increase of acidity of peripheral blood, especially in certain regions of the body subject to relatively inactive circulation at this time.

In 1 case (case 4) typical nocturnal hemoglobinuria had been observed before splenectomy. After splenectomy the nocturnal element of the hemoglobinuria was eliminated without alteration of the fundamental abnormality of the red blood cells or significant decrease of the anemia. Destruction of red blood cells is thought to occur within the splenic pulp, where anatomic and physiologic observations²⁹ have demonstrated ample opportunity for stasis. It appears likely, therefore, that splenectomy in this case had removed an organ which previously had provided a region of stasis during sleep and apparently a region of acidity even greater than the acidity of the peripheral blood. Increased stasis during sleep, therefore, especially in the spleen, may provide in part the increased acidity responsible for the nocturnal element of hemoglobinemia and hemoglobinuria.

29 McNee, J W. Spleen. Its Structure, Functions and Diseases (Lettsomian Lecture), *Lancet* 1 951, 1009 and 1063, 1931.

TABLE 10 —*Diagnostic in Vitro Tests for Chronic Hemolytic Anemia with Pavorusmal Nocturnal Hemoglobinuria*

Tube No	Treatment of Serum (Fresh Serums from Patient or from Normal Subject† of Same Blood Group)	Hemolysis*		Comment
		Patient's Red Blood Cells (5 per cent sus- pension in serum) Percentage	Normal Red Blood Cells (5 per cent sus- pension in serum) Percentage	
1	Unaltered serum	0 10	0	Patient's cells may or may not be hemolyzed by unaltered serum containing no added acid
2	Acidified serum (0.95 cc serum + 0.05 cc 1/3 normal HCl)	2 30	0 ±	Patient's cells always hemolyzed by acidified serum, no hemolysis of normal cells
3	Heat inactivated acidified serum (0.95 cc serum heated at 56° C for 5 minutes + 0.05 cc 1/3 normal HCl)	0	0	Heated serum (acidified) produces no hemolysis
4	Heat inactivated serum (acidified) + guinea pig complement (0.75 cc serum heated at 56° C for 5 minutes + 0.05 cc 1/3 normal HCl + 0.20 cc undiluted guinea pig serum)	0	0	The addition of large amounts of guinea pig complement does not restore the hemolytic activity of heated serum ⁵ .

* Samples incubated for 1 hour at 37.5° C

† Normal serum gave the same hemolytic reactions as did the patient's serum

No satisfactory form of therapy was found for this disease. The use of alkaline salts was complicated by severe hemolytic episodes on their withdrawal or during their administration. Acid-forming salts increased hemolysis temporarily and are potentially dangerous in producing damage of the renal tubules by precipitation of hemoglobin.³⁰ Splenectomy in the 2 cases observed did not decrease the anemia. Anti-syphilitic therapy administered to the patient in case 3 did not alter the course of the disease. Transfusions are usually associated with hemolytic reactions of varying severity but also are followed by periods ranging from several days to weeks during which the rate of intravascular hemolysis is strikingly decreased, as evidenced by low levels of hemoglobin in the plasma and in the urine and by increase of the red blood cell and hemoglobin content of the peripheral blood. In one instance (case 3) a transfusion reaction was followed by oliguria and uremia. Transfusions may be used guardedly as supportive measures. Conservative treatment consists of administration of iron by mouth, a good diet, moderate activity and avoidance of infections.

This disease has received many names, with resulting confusion in classification. As has been suggested by Hamburger and Bernstein, the term "chronic hemolytic anemia" certainly describes one essential feature of the syndrome. However striking may be the appearance of "paroxysmal nocturnal hemoglobinuria," it must be emphasized, first, that hemoglobinemia was present continuously in all cases and is a fundamental feature of this disease, second, that hemoglobinuria undoubtedly results from the excretion of the free hemoglobin circulating in the plasma, third, that hemoglobin may be absent from the urine for intervals varying from days to weeks, and fourth, that an increase in the hemoglobin content of the plasma during sleep ("nocturnal") was always observed in patients with intact spleens even when the urine was free from hemoglobin. Therefore, hemoglobinuria is not a true index of the concentration of hemoglobin in the plasma. For these reasons this disease might be described more accurately by the term chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia.

SUMMARY AND CONCLUSIONS

In chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Mairchiavava-Micheli disease) the fundamental abnormality resides in the red blood cells.

30 DeGowin, E. L., Warner, E. D., and Randall, W. L. Renal Insufficiency from Blood Transfusion. II. Anatomic Changes in Man Compared with Those in Dogs with Experimental Hemoglobinuria, *Arch. Int. Med.* **61**: 609 (April) 1938.

A thermolabile factor essential for hemolysis was found in the plasma and serum of 5 patients and of all normal subjects examined

The patients' plasma and serum exhibited no hemolytic action on normal cells

In vitro, the patient's washed red blood cells suspended in plasma or serum from the patient or from normal subjects were hemolyzed frequently but not always at a normal p_H , hemolysis was always produced by increasing the acidity of plasma or serum within or beyond the physiologic range of variation in p_H , hemolysis was diminished or eliminated by decreased acidity

In vivo, free hemoglobin was present at all times in the plasma, indicating continued intravascular hemolysis. Increased acidity produced by ingestion of acid-forming salts was associated with a transient increase in hemoglobinemia and hemoglobinuria in 2 of 3 cases. Alkalosis produced by ingestion of alkaline salts and by hyperventilation was associated with a transient decrease in hemoglobinemia and hemoglobinuria

Nocturnal hemoglobinemia was associated with sleep and not with the patient's posture, with ingestion of food or fluid or with the time of day or night during which sleep occurred. It is suggested that increased hemoglobinemia and hemoglobinuria during sleep are induced by increased intravascular hemolysis associated with increased acidity of blood, especially of regions of the body subject to stasis, such as the spleen

Splenectomy in 2 cases did not alter the fundamental abnormality of the red blood cells or decrease significantly the anemia. In 1 patient studied before and after splenectomy removal of the spleen was associated with elimination of the rise in hemoglobinemia and hemoglobinuria during sleep

Administration of alkaline salts was unsatisfactory as a therapeutic measure, withdrawal of the therapy producing severe and prolonged hemoglobinemia and hemoglobinuria

The blood picture, laboratory findings and clinical records in 5 cases are reported. Four of the cases have not been previously reported

It is suggested that this disease be called chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia

APPENDIX REPORT OF CASES

CASE 1—A Canadian-born school boy aged 17 was admitted to the Boston City Hospital in March 1937

History—The patient was in good health until the age of 15, when, in 1935, he first noticed shortness of breath on exertion, increased fatigability and listlessness for several months preceding an attack of influenza which was followed by the development of pallor with moderate jaundice, symptoms which continued to

the time of examination. He was anemic, there being 2,620,000 red blood cells per cubic millimeter, with 50 per cent hemoglobin. This condition was first observed in March 1936, and has continued, with periods of increased severity, to the time of this report. The urine was first observed to be "the color of blood" after a second infectious episode, with fever, cough and prostration, in June. During this period the urine was dark red continuously for several days. There were no further observations on the color of the urine. For the subsequent eight months the patient was chronically ill with varying degrees of jaundice. The red blood cell count varied from 1,240,000 to 1,770,000 per cubic millimeter. During this interval one transfusion was given, without apparent reaction and with some benefit. In addition, large doses of liver extract by intramuscular injection were administered, together with large amounts of raw liver, desiccated hog stomach (ventriculin) and iron given by mouth. During the three months before admission the jaundice had decreased and the patient was ambulatory, with a good appetite and few complaints other than pallor and easy fatigability.

Past History—At the age of 12 the patient had pneumonia on the left side, with pleurisy but without known sequelae. In 1935, after a body blow, he noted "smoky" urine for one day only.

Family History—There was no familial history of anemia, jaundice or hemoglobinuria. The patient's mother had hay fever and diabetes mellitus, his maternal grandmother had had asthma. Four siblings were well.

Physical Examination—The patient was athletic and well nourished. He was pale, with moderate icterus of the scleras and light yellowish brown tinting of the skin. There were papular eruptions of acne on the face and healed scars over the shoulders. The temperature and the pulse rate were normal. The blood pressure was 120 mm of mercury systolic and 65 mm diastolic. There was a systolic murmur over the apex of the heart.

Laboratory Observations—As has been mentioned, large amounts of hemoglobin were excreted in the urine, especially after sleep, with or without hemoglobinuria during waking hours (chart 2). For periods of from three days to two weeks the urine was entirely free from hemoglobin. Hemoglobinemia was always present (charts 2 and 3). The laboratory observations concerning the blood are summarized in table 1. The specific gravity of the urine varied from 1.002 to 1.035. There was a trace of albumin in specimens containing no hemoglobin. The sediment of the urine showed no red blood cells, occasional casts, constantly present hemosiderin and moderately increased urobilinogen, but no bile. The stools contained no occult blood. The Takata-Ara reaction was negative. The van den Bergh reaction was indirect. The calcium content of the serum was 9.6 mg, the phosphorus content 5.5 mg and the vitamin C content 0.5 mg per hundred cubic centimeters, the basal metabolic rate was +12 per cent. The gastric contents after injection of histamine yielded 57 units of free acid. Cutaneous tests showed no sensitivity to pollens, food or certain other test substances. Roentgen examination revealed no abnormalities of the skull or chest, the long bones were normal except for a post-traumatic osteoma of the right tibia. Culture of pus expressed from an acne lesion showed *Staphylococcus aureus*.

Progress—After periods during which the urine was free of hemoglobin, nocturnal hemoglobinuria returned without apparent cause and without other symptoms or signs. Hemolytic episodes of varying severity were associated with (1) an infection of the upper respiratory tract, (2) oral administration of 10 Gm of ammonium chloride daily for two days, (3) intravenous injection of 1 Gm of unneutralized ascorbic acid, (4) a febrile reaction to the eighth consecutive daily

intramuscular injection of 5 cc of liver extract (liver extract-Lilly N N R), (5) withdrawal of alkali therapy (40 Gm sodium bicarbonate given by mouth daily) and (6) transfusion of 500 cc of citrated blood. Severe hemolytic episodes were not necessarily associated with fever or chills but were always associated with some fatigue, there was no pain, dysuria or nausea. Transfusion was followed by a febrile reaction for twenty-four hours, with extreme hemoglobinemia and hemoglobinuria during the second and third days after transfusion. Hemoglobin disappeared from the urine on the third day, with a striking decrease in hemoglobinemia and hemoglobinuria. Hemoglobinuria was absent for two weeks, returning in slight amounts nocturnally in the subsequent two weeks. No apparent benefit was observed after the intramuscular injection of liver extract, the intravenous and intramuscular injection of 1 Gm or 0.5 Gm daily of ascorbic acid and the oral administration of iron and of liver extract (Valentine).

In the sixteen months since the patient's discharge from the hospital, in August 1937, he has returned to Canada and successfully continued his studies at boarding school. Except for acute attacks he has usually felt well, taking part in moderate exercise and enjoying normal activity with the limitation of somewhat increased fatigability. The disease has remained unchanged, however, the blood count varying from 1,510,000 to 2,410,000 red cells per cubic millimeter and the concentration of hemoglobin from 38 to 53 per cent. Five infections of the respiratory tract, including purulent otitis media, produced severe hemoglobinuria in 4 instances. Four transfusions were followed by from three to four days in which the urine was dark red and a subsequent period of from three days to three weeks without apparent hemoglobinuria. The only treatment other than transfusion has been administration of ferrous sulfate by mouth, 12 grains (0.78 Gm) per day.

CASE 2—A woman aged 39, a minister's wife living in New Hampshire, was admitted to the Boston City Hospital in October 1937.

History—The patient felt well until the summer of 1934, when the insidious onset was noted of increased fatigability, palpitation and pallor. No jaundice was present. There were no other symptoms. Slight jaundice was observed in November 1934, together with anemia. The latter condition had been treated with large amounts of liver extract given parenterally and of liver extract and iron given by mouth, without apparent benefit.

In the subsequent three years preceding her admission to the hospital the patient showed chronic anemia and intermittent jaundice. The urine on occasions was red or black, especially after sleep, exacerbations appeared to follow infections of the respiratory tract and indigestion associated with ingestion of fat. During acute episodes the patient remained in bed because of fatigue and palpitation, at other times she was able to partake in moderate activity. The maximum red cell blood count observed in this period was 2,500,000 per cubic millimeter, and the maximum concentration of hemoglobin was 65 per cent. The resistance of the erythrocytes to hypotonic saline solutions was normal. Serologic tests for syphilis gave negative results. Analysis of the gastric contents after a test meal revealed free hydrochloric acid. Several therapeutic regimens were without striking benefit, namely, a Sippy diet with alkaline powders, large doses of iron by mouth and a second series of intramuscular injections of liver extract.

Past History—Sore throat associated with moderate fever, lymphadenitis of the neck and prostration for from two to three days had occurred approximately once each winter for many years. Menstruation had been normal. There had been no pregnancies.

Family History—There was no familial history of anemia, jaundice or hemoglobinuria. Two siblings had died at 25 and at 30 years of age respectively of pulmonary tuberculosis. A third had died at the age of 30 of heart disease. Four siblings were well.

Physical Examination—The patient was slight in stature but was well developed and well nourished. She appeared to be in good health except for moderate pallor and a slight brownish yellow tint to the scleras. The temperature and pulse rate were normal, the blood pressure was 130 systolic and 60 diastolic. A rough systolic murmur was heard over the apex of the heart. The tip of the spleen was palpable.

Laboratory Observations—The laboratory observations concerning the blood are summarized in table 1. The maximum specific gravity of routine specimens of urine was 1.023, a trace of albumin was found in specimens containing no hemoglobin, the sediment contained hemosiderin, occasional casts and white and red blood cells. The stools showed no occult blood. The Takata-Ara reaction was negative. The basal metabolic rate was +6 per cent. Roentgen examination of the chest showed small areas of calcification at the apices of both lungs, compatible with healed tuberculosis. Roentgen examination of the abdomen revealed moderate splenomegaly.

Progress—During one week of observation the patient received no therapy other than the administration of iron by mouth. She had never received a transfusion.

In the year since her discharge from this hospital there have been no major hemolytic episodes, but the patient has noted bouts of nocturnal hemoglobinuria. She maintained moderate activity.

CASE 3—An Italian man aged 48, an unemployed contractor, was admitted to the Boston City Hospital in April 1938, which was fourteen months before his death in July 1939.

History—This patient enjoyed good health until February 1934, when he complained of intermittent dull pain in the lumbar region, radiating to the abdomen and to the left testicle and associated with the passage of red urine.

In the subsequent four years he was admitted to another hospital on four occasions (in 1934, 1936 and 1937). Throughout this period there were intermittent attacks of hemoglobinuria associated with symptoms of fatigue, vague malaise, occasional dysuria and frequency of voiding, pallor and moderate jaundice. Physical examination revealed moderate splenomegaly.

Chronic anemia was present at all times, the number of red blood cells varying between 2,290,000 and 3,790,000 per cubic millimeter and the hemoglobin content between 40 and 70 per cent. The urine always showed white cells and frequently showed hemoglobin, but without red blood cells. The urine concentration test showed the maximum specific gravity to be 1.020. A maximum nonprotein nitrogen content of 80 mg. per hundred cubic centimeters was observed in 1934, the maximum value was 30 mg. in 1937. Determinations of phenolsulfonphthalein in the urine after intravenous injection of the dye showed diminished total excretion after sixty-five minutes, 13 per cent in 1934 and 25 per cent in 1937. Values for serum bilirubin of 2.5 mg. and 2.2 mg. were observed in 1936 and 1937 respectively. Cystoscopic and retrograde pyelographic examination showed no abnormality of the bladder, ureters or kidneys. Roentgen examination of the chest and gastrointestinal tract revealed no abnormality. One of four Hinton tests was reported as giving a slightly positive result. The patient received antisyphilitic therapy.

without benefit to the anemia and with the development of severe jaundice and of stomatitis. A total of four doses of bismuth salicylate and nine doses of arsphenamine was administered. The Donath-Landsteiner reaction was negative, and chilling of the arm did not produce a hemolytic episode.

Past History—The patient had lived in Italy until the age of 17. There was no history of malaria. Gonorrhea was contracted at the age of 20 and apparently again in 1935. Before the present illness, as much as a pint of whisky and a bottle of wine had been consumed daily for several years.

Family History—There was no familial history of anemia, jaundice or hemoglobinuria. Seven siblings were well. Nine children of the patient were well.

Physical Examination—The patient was well developed and well nourished and appeared in good health except for moderate pallor and slight icterus of the sclerae. The pupil of the left eye was deformed owing to trauma. The temperature and the pulse rate were normal. The blood pressure was 150 systolic and 90 diastolic. The tip of the spleen was palpable.

Laboratory Observations—The laboratory observations concerning the blood are summarized in table 1. The maximum specific gravity of routine specimens of urine was 1.020. A heavy trace of albumin was present in specimens containing no hemoglobin, the sediment showed hemosiderin, casts, white blood cells and rare red blood cells. The stools showed no occult blood. The Takata-Ara reaction was negative.

Progress—During the fifteen months before death the patient was admitted to the Boston City Hospital on four occasions for a total period of one year. Throughout the patient's hospitalization the urine contained hemoglobin in varying amounts except on the following occasions: in five instances after transfusion of 500 cc of citrated whole blood, in two instances after transfusion of washed red blood cells derived from 500 cc of whole blood, on one of two occasions after intramuscular injection of washed stroma prepared from washed red blood cells, and for several periods of two to three weeks during the active stage of pyelonephritis, which was present for the five months preceding his death. In the aforementioned instances the hemoglobinemia decreased strikingly, and the hemoglobinuria disappeared entirely for two to four days, or for longer when associated with the renal infection. This was followed by the gradual return first of nocturnal hemoglobinuria and then of hemoglobinuria at all times, the greatest excretion occurring during sleep. A severe hemolytic episode occurred coincidentally with an infection of the upper respiratory tract. Moderately severe hemolytic episodes occurred associated with abscesses of two molar teeth and their removal, for from two to three days after transfusion of citrated whole blood or of washed red blood cells and after the intravenous injection in divided doses during two days of 80 cc of a 50 per cent suspension of stroma from red blood cells in physiologic solution of sodium chloride. Clinically the patient was ambulatory, complaining only of moderate fatigue until the onset of acute pyelonephritis, which was evidenced by fever, frequency of urination and the finding in the urine of masses of pus cells and the colon bacillus. Ammonium chloride (4 Gm) and ammonium mandelate (12 Gm) administered daily for six days did not produce hemoglobinuria or an increase in hemoglobinemia. This therapy failed to decrease the p_H of the urine below 6.0 and also failed to reduce the pyuria and bacilluria. On the sixth day of this treatment progressive left hemiplegia developed, with incontinence of urine and feces. In the subsequent three months before death there occurred thrombosis of the left femoral vein, oliguria and uremia following trans-

fusion and decubitus ulcers over the sacrum. The value for nonprotein nitrogen increased to a maximum level of 230 mg per hundred cubic centimeters sixteen days after transfusion.

Autopsy—On gross examination the kidneys were of normal size and showed multiple small abscesses involving the cortex and tubular portions of the medulla between the pyramids. These areas were uniformly dark brown and gave a strong prussian blue reaction. The liver weighed 2,100 Gm, appeared reddish brown on section and showed a small area of recent infarction. The wall of the gall-bladder was thickened. The common bile duct contained several small black calculi but was not obstructed. The spleen weighed 560 Gm and on section revealed dark red soft pulp and a small infarct. The heart was normal. The lungs were edematous. There were fibrous pleural adhesions involving the upper lobe of the right lung. Thrombophlebitis involved the left femoral, saphenous and external iliac veins. The brain showed a large cystic area of softening involving a portion of the right internal capsule, the claustrum and a small portion of cerebral cortex. The bone marrow from the vertebrae, sternum, ribs and femurs was dark red and cellular. The tibial marrow was dark red but contained scattered areas of fat. There was a decubitus ulcer over the sacrum.

On microscopic examination the kidneys showed multiple areas of abscess formation, large deposits of hemosiderin confined to the tubular epithelium of the cortex and hemoglobin casts filling many of the collecting tubules. The liver revealed varying degrees of congestion of the central vein of the lobule, with atrophy of liver tissue and distention of the hepatic sinusoids and a moderate amount of atrophy of the hepatic cords. There were small areas of focal necrosis. The spleen contained an area of infarction and necrosis. Hemosiderosis was observed only in the kidney.

The bone marrow showed hyperplasia of the red cell series, except that from the tibia, which contained only occasional islands of hemopoietic tissue.

CASE 4—A man aged 32, an unemployed automobile mechanic, single, living in Virginia, was admitted to the Boston City Hospital in 1937.

History—The first deviation from health occurred in 1932, when the urine on three occasions, once in March, once in August and once in November, was observed to be dark with a heavy sediment. Lack of energy, increased fatigability, palpitation and dyspnea on exertion developed insidiously during this period. Anemia was present, a count of 2,500,000 red blood cells per cubic millimeter with 50 per cent of hemoglobin was observed as early as January 1933.

As was reported in detail by Hamburger and Bernstein,¹ this patient was observed in the Johns Hopkins Hospital in 1933 and in the Memorial Hospital in Richmond, Va, each year from 1933 through 1938, splenectomy was performed at the Hospital of the University of Pennsylvania in March 1935.

Throughout this period the patient was unable to work because of fatigue, and weakness. These conditions have persisted to the time of writing. He continued to show intermittent attacks of hemoglobinuria, chronic anemia and variable icterus. Splenectomy did not reduce the anemia. A total of fifty-three transfusions of whole blood had been given up to September 1937, associated with reactions of variable severity.

During the aforementioned periods of observation the number of red blood cells varied from 1,600,000 to 2,700,000 per cubic millimeter and the hemoglobin content from 30 to 52 per cent. The reticulocyte count was constantly elevated and was as high as 39 per cent. Before splenectomy the number of white blood cells varied

between 4,050 and 9,000 per cubic millimeter, after splenectomy the level was usually higher. Serologic tests for syphilis repeatedly gave negative results, as did repeated observations of the Donath-Landsteiner reaction. The gastric juice contained free hydrochloric acid after injection of histamine. The urine continued to show hemoglobin, but the nocturnal element apparently disappeared, as has been mentioned (chart 5). Roentgen examination of the long bone revealed no abnormality. Cutaneous tests with a variety of substances were without reaction.

Various forms of treatment were without permanent benefit, namely, transfusions of whole blood, parenteral administration of liver extract, a short course of injections of neoarsphenamine, intramuscular injections of antivenin, intramuscular injections of ascorbic acid and the oral administration of desiccated hog stomach (ventriculin), iron, calcium gluconate and liver extract.

At operation (1935) the spleen weighed 360 Gm. The sinuses contained a moderate amount of blood. The splenic pulp was normal. The postoperative course was complicated by otitis media and by mastoiditis requiring mastoidectomy.

Past History—At the age of 14 the patient had two attacks of multiple cutaneous boils. One small boil recurred in 1934. The following operations were performed: tonsillectomy in 1919, dental extractions in 1930, 1934 and 1936, adenoidectomy in 1933, and splenectomy in 1935. Before the present illness the patient had been exposed to carbon monoxide during automobile repair work and had occasionally noticed headache.

Family History—There was no familial history of anemia, jaundice or hemoglobinuria. One sibling died at the age of 19 of Bright's disease, 3 siblings were well.

Physical Examination—The patient was short, stocky, well developed and well nourished. He did not appear ill. The skin was of uniform brownish hue, and the scleras showed a similar brownish tint. The temperature and pulse rate were normal. The blood pressure was 108 systolic and 70 diastolic.

Laboratory Observations—The laboratory observations concerning the blood are summarized in table 1. During two months' study the urine was never free of hemoglobin. The nonprotein nitrogen content of the blood was abnormally elevated to a maximum of 72 mg. per hundred cubic centimeters, usually varying between 45 and 64 mg. The urine contained a heavy trace of albumin but the specimens showed small amounts of hemoglobin, the sediment revealed casts and hemosiderin. The stools showed no occult blood. The Takata-Ara reaction was weakly positive. The gastric juice after injection of histamine contained 28 units of free hydrochloric acid.

Progress—During mild hemolytic episodes the patient noted fatigue, anorexia, epigastric discomfort and indigestion. In the five years of his illness multiple transfusions of whole blood were used as the major therapy, from one to three per week being administered at intervals of from six weeks to several months. Three transfusions of 500 cc. each of citrated whole blood were given on alternate days during observation at this hospital. The maximum temperatures after the transfusions were 102.4 F, 102.4 F and 99.4 F, respectively. The patient was in a severe hemolytic episode at the time of the transfusions and continued to show extremely elevated levels of hemoglobin in the plasma and in the urine until twenty-four hours after the third transfusion, from which time the hemoglobinemia and hemoglobinuria decreased during the subsequent five days to the lowest levels observed in two months. The red blood cell count rose from 1,710,000 to 3,550,000 per cubic millimeter and the hemoglobin content from 39 to 60 per cent after these

transfusions The percentage of reticulocytes dropped from 10 to 3 Subjectively, the patient felt much improved Since his discharge from this hospital the course of the disease has remained unaltered

CASE 5—A woman aged 30, a housewife, living in Pennsylvania, was observed for two days in Boston in November 1938

History—The patient's first symptoms of illness occurred in 1931, at the age of 23, in Germany, when pallor with slight jaundice developed in association with her first pregnancy Delivery was complicated by postpartum hemorrhage, after which the level of hemoglobin was observed to be low and iron was administered In all subsequent examinations of the blood, made each year, anemia had been present, the value for hemoglobin usually being approximately 50 per cent A second pregnancy (in 1934) was uneventful except for the finding post partum of a hemoglobin level of 45 per cent A transfusion at this time was followed one week later by headache, abdominal pain, nausea, vomiting and jaundice In 1935 the removal of a sebaceous cyst was complicated by erysipelas In 1936 the patient had two attacks of violent pain in the right upper quadrant of the abdomen, described as gallbladder colic associated with moderate jaundice Because of anemia the patient received four blood transfusions In April 1937 the spleen was removed Six direct transfusions of whole blood were given, without apparent reaction After operation the anemia continued unaltered, with intermittent moderate jaundice usually associated with an infection of the upper respiratory tract During such episodes the patient felt fatigued and was required to rest most of the day At other times she carried on moderate activity

On one occasion after an infection of the respiratory tract in October 1938, the urine was grossly red On close questioning the patient recalled other periods of several days during which the urine had been dark, but nocturnal increase had not been observed

Various forms of treatment were without lasting benefit, namely, transfusions, intramuscular injection of liver extract and oral administration of liver extract and of iron

Past History—Tonsillectomy had been performed at the age of 18

Family History—The paternal grandfather apparently had a palpable spleen without anemia There was no familial history of anemia, jaundice or hemoglobinuria

Physical Examination—The patient was well developed and well nourished She appeared pale and slightly jaundiced The temperature and the pulse rate were normal The blood pressure was 110 systolic and 70 diastolic The edge of the liver was palpable on deep inspiration

Laboratory Observations—The laboratory observations concerning the blood are summarized for the years 1937 and 1938 (table 1) Two specimens of urine observed at this hospital on November 18 were dark red, containing large amounts of hemoglobin (without red cells) and a heavy precipitate of hemosiderin At this time free hemoglobin was observed in the plasma There was no opportunity to observe the influence of sleep In previous examinations the specific gravity of the urine had varied from 1.012 to 1.023 The urine showed a heavy trace of albumin and occasional red blood cells The urine was amber The stools contained no occult blood The basal metabolic rate was -4 per cent The gastric juice contained a normal amount of free acid Drainage of the biliary tract revealed no abnormality Roentgen examination showed no abnormality of the chest, gastro-

intestinal tract, gallbladder, kidneys or ureters At operation in 1937 the liver and gallbladder were normal and the spleen weighed 260 Gm , microscopically the spleen showed no increase in pigment and only a slight deviation from normal in the prominence of reticulum cells in germ centers

Dr William B Castle and Dr John H Dingle made important suggestions The observations on porphyrins are the work of Dr Robert Kark Miss Constance Brooks gave technical assistance Observations of the hydrogen ion concentration of blood and of the carbon dioxide and oxygen content of blood were made by permission of Dr David B Dill by his associates Dr Jost Michelson and Dr C Daly of the Fatigue Laboratory, Harvard University Study of the patient in case 4 was by permission of Dr William B Porter, Richmond, Va , the data in case 5 were supplied by Drs Thomas Fitz-Hugh Jr and William U McClenahan, Philadelphia

DIAGNOSIS OF HYPERSENSITIVENESS TO THE BEE AND TO THE MOSQUITO

WITH REPORT ON SUCCESSFUL SPECIFIC TREATMENT

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The animals which are harmful to man include a wide range. The predatory mammals which choose man as an article of diet are referred to mainly in writings on adventure. As one descends to the Reptilia, however, one finds much written on the venoms of snakes and other members of this group. Still farther down the scale come the Arthropoda, including, besides the spiders, scorpions, ticks and other arachnids, the immense and fascinating array of insects about which countless volumes have been contributed to scientific libraries. As one proceeds downward through the predatory worms, one comes to the lowest of all, the Protozoa, important agents of harm, either through their own activity or by collaboration with insects or higher animals.

The present consideration will be confined entirely to the class Hexapoda, or insects, which includes, according to various entomologists, thirty or more orders. Of these I need mention only a few, together with important examples: Anoplura (sucking lice), Hemiptera (true bugs), Trichoptera (caddis flies), Lepidoptera (moths), Diptera (flies and mosquitoes), Siphonaptera (fleas) and Hymenoptera (bees, wasps and ants) embrace most of the genera which interest physicians.

The study of allergy is probably not concerned with the role of insects as primary or secondary hosts for numerous human parasites, including Vermes, trypanosomes, Protozoa, lower plant forms and unknown viruses. These belong to the fields of bacteriology and parasitology. Neither does this study include the essential effects of venoms and poisons. These assume importance only as they carry with them sensitizing substances, either from the insect itself or by contamination.

A knowledge of entomology is essential to a real understanding of the harmful effects of the insects. Of the works consulted one of the

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most instructive has been Snodgrass' ¹ volume in the Smithsonian Institution Series, which, without being encyclopedic, contributes much valuable information on the life habits of the class. Other works consulted included Snodgrass' ² book on the honeybee, Matheson's ³ on mosquitoes and the book "Insects" in the Western Nature Study Series ⁴. Several other general publications on entomology were found useful.

The insects which produce allergic phenomena may be divided into three groups according to whether they sensitize the human host (1) innocently, by scales or dust shed from the wings or body, (2) by injection of venom through the sting situated in the rear extremity, or (3) by instillation of salivary secretion through the mouth parts. Each of these will be considered. The first group includes chiefly certain nonpredatory orders, especially Lepidoptera (moths and butterflies), Trichoptera (caddis flies) and Ephemeroidea (May flies). The second group includes various stinging members of Hymenoptera, notably the bees, wasps and ants. The third group embraces a wide range of blood-sucking pests, chiefly among the orders Anoplura (sucking lice), Hemiptera (true bugs), Diptera (flies and mosquitoes) and Siphonaptera (fleas).

Nearly all insects have the same essential mouth parts, but with marked variations. The parts consist of the labrum (upper lip), the mandibles (upper jaw), the maxillas (lower jaw) and the labium (lower lip). They may, as in the Lepidoptera, be fashioned into a siphon for sucking nectar, or they may be employed, as with many species, for chewing food, but in the predatory group they are rearranged to form a piercing needle for drawing blood.

The accompanying diagrams of the mosquito (fig. 1) will serve to illustrate the mouth parts of most blood-sucking species. The proboscis is a slender hollow needle formed by close apposition of the mandibles, maxillas, labium and hypopharynx. Body lice have a piercing and sucking mouth for drawing blood. Fleas likewise have an oral tube for piercing the skin, and the stable fly has a short broad proboscis formed by the usual combination of mouth parts. In the bedbug and other Hemiptera the mandibles and maxillas form piercing stylets enclosed in a tube formed chiefly by the labrum.

1 Snodgrass, R. E. *Insects: Their Ways and Means of Living*, New York, Smithsonian Institution Series, Inc., 1930.

2 Snodgrass, R. E. *Anatomy and Physiology of the Honey-Bee*, New York, McGraw-Hill Book Company, 1925.

3 Matheson, R. *A Handbook of the Mosquitoes of North America*, Springfield, Ill., Charles C. Thomas, Publisher, 1929.

4 Pickwell, G., and others. *Insects*, Natural Science Department, California State Teachers College, Western Nature Study Series, Los Angeles, Suttonhouse Ltd., Publishers, 1933.

The Hymenoptera which threaten man and animals by their sting have an anatomic setup designed for their special needs. The mouth parts are usually inoffensive and adapted to lapping nectar or chewing pollen and other foods. The stinging mechanism, situated in the rear end of the animal comprises an elaborate offensive and defensive apparatus (fig 2) formed by the adaptation of the ovipositor. Through its hollow double lancet is injected the venom, a highly complex mixture of chemical ingredients, the probable nature of which in the bee has been considered in a previous report.

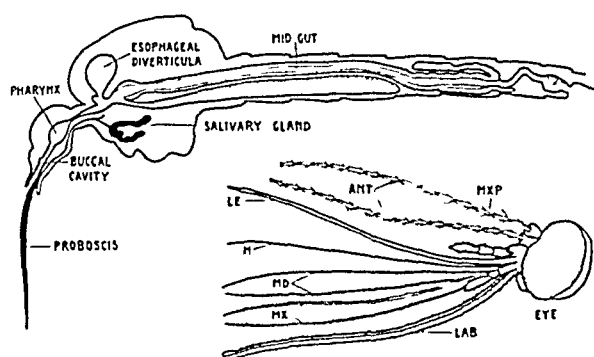


Fig 1—The mouth parts of the mosquito

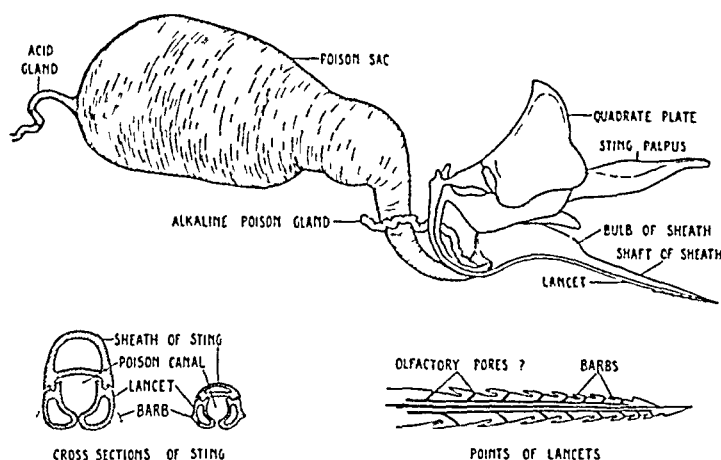


Fig 2—The stinging mechanism of the honeybee

I INHALATION OF EMANATIONS FROM INSECTS

Coca and his associates⁵ stated that Ancona, in 1922, described an epidemic asthma which, at certain times, occurred among cereal workers in Italy as a result of handling grain infested with the larvae of *Pediculoides ventricosus* and that Van Leeuwen reported a similar condition in Holland. Coca, however, regarded these reactions as non-specific.

⁵ Coca, A. F., Walzer, M., and Thommen, A. A. Asthma and Hay Fever in Theory and Practice, Springfield, Ill., Charles C. Thomas, Publisher, 1931.

In 1929 Parlato⁶ reported an instance of rhinitis and asthma due to the emanations of the sand fly, or caddis fly, an insect of the order Trichoptera abounding along Lake Erie and the Niagara River. The following year, in a routine study of 192 allergic patients,⁷ he found that 14 reacted to filtered extracts of the same species by intracutaneous and ophthalmic tests. Passive transfer by the Prausnitz-Kustner technique was successful in the 4 cases in which it was tried. At about the same time Figley⁸ recorded 4 cases of asthma due to the pellicles shed by the May fly, a member of the order Ephemera which swarms about Toledo, Ohio.

In 1929 Sternberg⁹ described the occurrence of asthma caused by *Cimex lectularius* (bedbug). Unfortunately no proof was available that sensitization arose from inhalation. Successful transfer by the Prausnitz-Kustner method with 1:1,000 extracts of the bug did, however, suggest the inhalation route. Such a high grade of sensitiveness is not usually observed when the allergic reaction arises from the bite. This point will be considered more extensively later.

Equally difficult to classify were the two cases reported by Ellis and Ahrens¹⁰ of reactions to emanations of bees. The first patient was definitely sensitive by scratch to venom, extracts of various portions of bees' bodies and pollen from hives, but not to ordinary pollen, wings of bees or stings. These apparent disagreements were difficult to explain. The second patient gave a history of asthma from the airborne products of the bee and also of sensitiveness to the sting. The findings in this case were inconclusive because of the patient's refusal to submit to adequate testing.

As might be expected, the Lepidoptera (moths), with their dust-laden wings, proved to be a cause of inhalation symptoms. Parlato¹¹ in 1932 described in detail the abundant dust shed by the wings of moths and reported an instance of hypersensitiveness. Later he announced passive transfer of the reagins of the caddis fly, butterfly and moth and found only a quantitative difference in the degrees of

6 Parlato, S. J. A Case of Coryza and Asthma Due to Sand Flies (Caddis Flies), *J. Allergy* **1** 35, 1929.

7 Parlato, S. J. The Sand Fly (Caddis Fly) as an Exciting Cause of Allergic Coryza and Asthma, *J. Allergy* **1** 307, 1930.

8 Figley, K. D. Asthma Due to the May Fly, *Am. J. M. Sc.* **178**:338, 1929.

9 Sternberg, L. A Case of Asthma Caused by the *Cimex Lectularius* (Bedbug), *J. Allergy* **1**:83, 1929.

10 Ellis, R. V., and Ahrens, H. G. Hypersensitiveness to Air Borne Bee Allergen, *J. Allergy* **3** 247, 1932.

11 Parlato, S. J. A Study of the Atopic Reagins of the Caddis Fly, Butterfly and Moth, *J. Allergy* **3**:125, 1932.

reactivity to extracts of the three types of insect Balyeat and his associates¹² also reported routine reactions to extracts of Lepidoptera

The only reference to nasal allergy from emanations of the house fly's wing is that of Jameson¹³ His patient reacted to scratch and to nasal instillation Passive transfer was successful

II SENSITIZATION TO STINGS OF HYMENOPTERA

In a previous publication Semenov and I¹⁴ reported an instance of extreme hypersensitiveness to the sting of the honeybee, presented a résumé of the more important literature and gave a detailed description of the bee's stinging mechanism and the reputed components of the venom I have subsequently encountered other examples of sensitization to Hymenoptera which I shall recite briefly

It is apparent that extreme reactivity to these insects is an acquired condition In reporting our first case we mentioned that the patient was a bee keeper who during his first year in the business suffered many stings, reputedly as many as seventy-five in one day, with no unusual harm During the second year he began to experience increasing distress with each sting, and by the end of the third year he became so ill after single stings that he feared having to abandon his occupation

In the meantime Beck¹⁵ presented his interesting plea for the venom therapy for rheumatic conditions, but admitted a lack of knowledge as to the method followed in the preparation of the antigen Of especial concern to us, however, was his recital of numerous minor or major casualties from stings of Hymenoptera, including information from lay sources and even from the daily press In spite of the variable and sometimes doubtful source of data the author presented a commendable volume of detail

It was easy to explain his reported death of an imbecile following stings so numerous that bees were passed by emesis and from the rectum and also the death of a man of 84 who received 1,200 stings His numerous instances of death from a single sting suggested anaphylaxis, but the theory lacked experimental proof Much more interesting were his many accounts of increasing sensitivity with repeated stings and his reported cases of generalized urticaria, sometimes bullous He also related examples of anaphylactic shock from isolated stings

12 Balyeat, R M , Stemen, T R , and Taft, C E Comparative Pollen Mold, Butterfly and Moth Emanation Content of the Air, *J Allergy* 3 227, 1932

13 Jameson, H C The House Fly as a Cause of Nasal Allergy, *J Allergy* 9 273, 1938

14 Benson, R L, and Semenov, H Allergy in Its Relation to Bee Sting *J Allergy* 1 105, 1930

15 Beck, B F Bee Venom Therapy, New York, D Appleton-Century Company, Inc , 1935

Necessarily these reports, like all the reports of death in the literature, lacked immunologic verification and left the exact cause of death in doubt

An adequate demonstration of specific sensitization to the sting of the bee must rest on the essential relation of antigen and antibody. Braun¹⁶ reported successful inoculations of increasing doses of material from bees in a patient who reacted to the sting of the insect, but unfortunately failed to obtain verification by cutaneous or other specific tests. Previous to our original report there was a dearth of evidence of definite reaction to extracts of bees followed by specific relief. I therefore decided to review once more the factors in hypersensitiveness to bees and other species of insects and to supply additional examples

Our previous report mentioned that the specific harmful effects of the Hymenoptera should be considered as possible results of sensitization to the venom itself, to pollen adherent to the bee's body or to allergens inherent in the insect. To these I shall now add atopic reactions due to inhalation of material shed by the bee. This conception has already been discussed in connection with the report of Ellis and Ahrens¹⁰

The venom of bees and other members of the Hymenoptera contains a complex poison which Wells,¹⁷ on the basis of Flury's¹⁸ study, interpreted as a possible combination of lecithin with basic radicals somewhat resembling sapotoxins and cantharidin. Whatever the chemical nature of the poison may be, it is of moderate toxicity to the human species, nonspecific and therefore tending to cause somewhat of a reaction in every one. The ordinary clinical symptoms appear in various works on medicine and toxicology. I am especially concerned here with the alarming and even fatal manifestations, which are tabulated in a book such as Beck's. It is obvious that a multiplicity of simultaneous stings might provide enough true poison to cause death. When, on the other hand, a person who has previously withstood repeated attacks of bees without harm later succumbs to the effect of a single sting, it is difficult to reject the suspicion that one is dealing with a specific phenomenon in sensitization.

The question whether venom itself can sensitize is obscured by a consideration which Wells¹⁷ raised. He ascribed a histamine-like action to the venom of bees. Semenov and I¹⁴ compared the effects of bee venom and of histamine on a strip of the virgin guinea pig's uterus. The

16 Braun, L. I. B. Notes on Desensitization of a Patient Hypersensitive to Bee Stings, *South African M. Rec.* **23** 408, 1925

17 Wells, H. G. *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1925

18 Flury, F. Ueber die chemische Natur des Bienengiftes. *Arch. f. exper. Path. u. Pharmacol.* **85** 319, 1920

strip of muscle responded to a solution of 1 part of bee venom in 100,000 parts of saline solution, and the tracing thus obtained corresponded closely with that given by histamine. It seemed highly probable that bee venom contained a substance resembling histamine. Considering the similarity of the effects of histamine and of anaphylactic bodies, the implications became still more confusing and the need of painstaking immunologic study appeared obvious.

In my study with Semenov we compared in a highly sensitive person the cutaneous scratch reactions to bee venom, the stinging apparatus and the substance of the bee's body. It developed that an extract of bee's bodies from which the stingers and poison sacs had been removed caused a reaction as strong as that to the insect's stinging mechanism or even the venom itself. The three effects were identical: 4 plus immediate wheals, as compared with scant 2 plus wheals with a 1:1,000 solution of histamine. Nonsensitive controls gave only a negligible reaction to the three products of the bee, but showed the usual non-specific reaction to histamine.

After a repetition of such experimentation, we concluded that the patient was definitely sensitive to extracts of the bee. This hyperreactivity was not due merely to the histamine-like effect of the venom, since the extract of the body without the poison apparatus produced the same wheal. Concentration of extracts with cold alcohol or a saturated solution of ammonium sulfate, to increase the percentage of protein, augmented the reactivity. Inoculations of such concentrates over an extended period resulted in a complete cessation of serious effects from multiple stings. We felt justified in concluding that the patient's sensitive state was due, not to the poison of the venom proper, but to the included body protein of the insect. In the seven years since publication of these results, an additional immunologic study has been conducted to clear up certain doubtful points. Coca⁵ made the very just criticism that passive transfer was needed. It also occurred to me that attention should have been given to the delayed reactions as well as to the early wheals. The possible role of pollens also demanded more study. The 10 additional cases here recorded will throw some light on these and on other problems.

All the patients were selected because they complained that stings produced large, hot, painful swellings which persisted for days, sometimes with general prostration. In 5 of them a sting constituted a definite hazard to life. The seventh patient's father, who was an agent for a pharmaceutical house, saw his son stung and described the onset of profound shock. He maintained that prompt administration of epinephrine alone prevented a fatal outcome.

The accompanying table includes, besides data on patient 1, previously described, data on the 10 additional patients subjected to immunologic study.

Data on Eleven Patients Subjected to Immunologic Study

No	Name	Sex	Age When Tested	Reaction to Inoculations			Degree of Clinical Sensitization	Sensitization to Pollens	Other Allergic Reactions	Clinical Diagnosis	Treatment for Bees
				Immediate	24 Hr						
1	E S	M	50	Bee Mosquito	++++ —		Prostration, pulmonary symptoms simulating pneumonia	Strong	None	Hay fever, allergy to bees	Course of inoculations of bee extract, with complete relief, 1929-30
2	J W	M	32	Bee Hornet	++++ —		Large and persistent swelling	Strong	None	Hay fever, allergy to bees	None
3	C W	F	19	Bee Hornet Mosquito	+++ ++++ +		Large and persistent swelling	None	Many foods and dusts	Asthma, allergy to bees	None
4	I I W	F	44	Bee	+++		Large and persistent swelling	Moderate	Hay, flax seed, mustard, etc	Asthma, allergy to bees	None
5	W C H	M	6	Bee	++	+++	Large and persistent swelling, urticaria, dyspnea	Negligible	Not tested	Allergy to bees	8 inoculations of bee extracts, 1935, stung 1937-1938, with ordinary small wheal resulting
6	H W G	M	49	Bee	+++	+++	Large and persistent swelling	Extreme	Many foods and dusts	Hay fever, vasomotor rhinitis, allergy to bees	None
7	A W	M	13	Bee Hornet	+++ —	+++	Extreme prostration, anaphylactic shock?	None	Not tested	Allergy to bees	14 inoculations of bee extract, 1934, and 9 in 1937, no subsequent stings
8	G L H	M	63	Bee Hornet Mosquito	+++ +++ +++	+++ +++ —	Large and persistent swelling	None	Many foods	Urticaria, allergy to bees	3 inoculations of extract of Hymenoptera, no subsequent stings
9	L W	M	44	Bee Yellow Jacket Hornet	+++ + +	+++ — —	Persistent large swelling with malaise and prostration later sloughing at site of sting	None	1. dermatitis house dust	Urticaria, eczema, headache, allergy to bees	One season's inoculations of bee extracts, no subsequent report
10	C F R	M	67	Bee Hornet Yellow Jacket	+++ + +	+++ + +	Collapse with unconsciousness for 5 minutes followed by urticaria	None	Not tested	Allergy to bees	One season's inoculations of bee extracts, no subsequent report
11	I M	F	62	Bee Vespa Mosquito	+++ +++ +++	+++ +++ +	Extreme and persistent swelling	Moderate	Not tested	Allergy to bees, dermatitis	7 inoculations of bee extract, no stings reported

Of the 11 patients, 5 consulted me because of the hazard attending an extremely violent response to single attacks of bees. It was my belief that these belonged probably in the same category as the subjects of unexplained death due to shock from single stings, as reported by Beck¹⁵. I therefore undertook to inoculate them repeatedly with bee extracts according to the technic formerly described¹⁴. In the previous report appeared a full description of the treatment of patient 1, a bee keeper who was dangerously sensitive to a single sting. After a course of inoculations for three months, he received on one occasion at least twenty-five simultaneous stings with no ill effects beyond local discomfort. On a subsequent occasion I personally observed the site of a sting which the patient had received a few hours before on the canthus of the eye and found no significant infiltration. I treated him only two seasons, but in the subsequent ten years he reported no serious consequences from stings. Patient 5 in 1935 received a course of eight inoculations. The following report received recently from his father, who is professor of pathology at the University of Oregon Medical School, indicates the apparent relief obtained:

Until the summer of 1937 my son escaped contacts with bees, so that there was no opportunity to learn the results of your desensitization treatment given in 1935. He was then stung by a honeybee with no more effect than a local reaction at the site of contact. The extreme allergic manifestations which he formerly had were entirely absent. Again in 1938 he received a sting without untoward result. I am most grateful to you for the striking results of the treatment given.

The other violent reactor, patient 7, and the casual reactor patient 8, have been treated but the efficacy is still to be determined. I do not yet feel justified in deliberately subjecting any of these subjects to the onslaughts of bees. As a result of the limited experience to date I feel confident, however, that the specific inoculations will prove a safeguard against the occasional alarming consequences of stings.

Of more import here are certain immunologic findings. Venom caused no stronger reaction in any of these sensitive patients than did the extracts of bees' bodies from which the stings and poison sacs had been removed. Thus patient 1, by the scratch test, gave 4 plus reactions to raw venom, to extracts of stings and poison sacs combined and to extracts of bees' bodies from which the poisonous rear ends had been removed. Patient 2 gave 4 plus reactions to extracts of bee stings and poison sacs combined, of whole bees' bodies and of bees' bodies from which the stings and poison sacs had been removed. All the other patients responded similarly. It seemed logical to conclude that in these allergic persons the specific phenomenon was due to some allergen inherent in the insects' bodies and that the sting caused sensitization only because its venom included, besides its ordinary poison, the identical allergen of the bees' protoplasm.

The nature of this antigen was further studied. I used many thousands of honeybees in the preparation of materials. The stings and poison sacs were plucked from one group, the remaining portions of the bodies being reserved for separate study. In another group the whole bees were used. In all instances the material was ground, dried, etherized to remove fats, extracted in physiologic solution of sodium chloride and subjected to the procedures ordinarily employed in making protein, namely, precipitation with cold alcohol or a saturated solution of ammonium sulfate. The resulting impure protein was washed repeatedly with cold alcohol and ether and dried to form a powder. Dialysis was of course used for ammonium sulfate precipitates. The resulting dry antigen formed the basis of most of my extracts. It was not necessary to assume that this fraction represented anything corresponding to pure protein. It was found, however, that the process of concentration increased the protein content of extracts and enhanced their potency. I became convinced that I had, in an impure form, a protein-bound antigen of the bees' bodies which was specific, non-dialyzable, thermostable and responsible for the type of violent phenomena which occasionally result from the sting of a single insect of the order Hymenoptera.

Pollen adherent to the bee might, through inhalation, account for certain symptoms in bee keepers, but could scarcely apply to the effects of stings with which I was dealing. The lancet of the bee carries no pollen with it, yet the tests proved conclusively that the stinging apparatus caused reactions as potent as those caused by the bees' bodies. More important still, 5 of my 11 patients were found nonsensitive to any of the pollens of the vicinity. I was forced to the conclusion that the allergen resided in the substance of the insects' bodies.

Most of the patients whose data were tabulated had in addition to their specific response to the products of the bee a definite atopy to foods or dusts or both. Clinically 3 had hay fever, 2 asthma and 1 urticaria. For some of them the routine of handling the atopic condition was so burdensome that I found it impossible to include a course of inoculations for bees.

The advantages of the intracutaneous testing became obvious when, in cases 5 to 11 inclusive, I supplemented the scratch test with this method. The early wheals were usually more pronounced than those following the scratch, but the chief advantage of the injection was that it produced delayed infiltrations which were red, warm, raised and painful and which persisted for days. I found that these were even more significant than the immediate reactions. Thus, patient 5 showed only a 2 plus wheal from the scratch and even from intracutaneous injection of 0.05 cc. of a 1:25 solution of extract of bee. The next day, however, at the site of injection there was a large, hot, itching swelling

which persisted for three days. In patient 6 the twenty-four hour infiltration was even more pronounced, occupying about one half of the flexor surface of the whole arm. In patient 8 both whole bee protein and stingerless bee protein, injected intracutaneously, caused large 4 plus wheals in fifteen minutes, and they increased greatly in another thirty minutes. The wheals next day were red and tender and measured 50 by 50 mm for the whole bee protein and 60 by 60 mm for the stingerless bee protein. All these late infiltrations were in general similar to those described for the mosquito (fig 3).

Passive transfer by the Prausnitz-Kustner technic has proved difficult and was omitted from our earlier report¹⁴. After unsuccessful attempts with several serums, I found that the serum of patient 6 was the only one which contained sufficient reagin for transfer. Of this



Fig 3—Twenty-four hour reaction to intracutaneous inoculation of a 1:50 dilution of the concentrate of the mosquito *Aedes vexans* in patient 4.

serum I injected 0.1 cc into each of two sites on a nonreactive subject. Two days later site 1 received 0.02 cc of a 1:50 solution of the extract of bee's sting apparatus and site 2 received a similar amount of extract of hornets of about the same titer. Control sites received equal amounts of the same antigens. Within fifteen minutes the site of the bee extract showed an irregular wheal measuring 14 by 11 mm, while its control failed to react. At the site of the hornet extract appeared a wheal measuring 16 by 11 mm, with a negligible reaction in its control. This experiment furnished ample evidence that the serum of this strongly reactive patient contained reagins for both the honeybee and the hornet. The twenty-four hour reaction failed to transfer.

One has therefore a single instance of passive transfer of the immediate reactions to the bee and to the hornet. The failure of other serums to cause the same phenomenon convinces me that hypersensi-

tivity to the Hymenoptera is not dependably transferable. This is not surprising in view of the fact that the important reaction reaches its maximum intensity in twenty-four to forty-eight hours. It is quite possible that one is dealing here with a distinct type of allergy which will exhibit the Prausnitz-Küstner phenomenon only as far as pronounced immediate wheals are concerned.

Sensitization to bees is, however, unquestionably a specific phenomenon. The foregoing successful passive transfer of the reaction to both the honeybee and the hornet by the same serum raised the question whether this patient had a group sensitivity to different Hymenoptera or whether he was independently sensitive to the two insects. Was it a species specificity toward each or a specificity toward the whole order? This question requires further study. Suffice it that 4 of my bee-sensitive patients (2, 7, 9 and 10) failed to react to the hornet and wasp, while 3 others (3, 8 and 11) showed the same 4 plus reaction to the bee and the hornet-wasp group. It is of interest in this connection that Ellis and Ahrens¹⁰ reported coincident reactions to honeybees and bumblebees.

In the meantime reports appeared on allergy to wasps and hornets. Hubert¹⁹ and Mantoux²⁰ published such reports without corroborative tests. Lincoln²¹ recently described an interesting example of acute shock from seven stings of yellow jackets but included no immunologic studies.

Sulzberger, in discussing my earlier paper²² on the mosquito, stating that the twenty-four hour reaction but not the immediate reaction, was abolished by reinjection in the same site, said

You can desensitize patients with comparative ease as far as the late twenty-four to forty-eight-hour papular reactions are concerned, whereas the immediate or wheal type reactions, although also due to hypersensitivity, are extremely difficult to influence and usually remain constant in spite of all desensitizing procedures.

With this statement I am in full accord.

Patient 7, who had a 3 plus wheal from 0.02 cc. of a 1:25 solution of the extract of whole bee, reacted on the following day with a 4 plus infiltration which measured 14 by 9.5 cm. and was hot, red and swollen. Three days later, when the reaction had subsided, he received a remoculation in the same site with 0.05 cc. of the same antigen. The

19 Hubert, E. Accidents anaphylactiques par deux piqûres de guêpe reçues à une heure d'intervalle, *Lyon med.* **138** 678, 1926.

20 Mantoux, C. Choc par piqûre de guêpe, chez un tuberculeux, *Presse med.* **36** 259, 1928.

21 Lincoln, M. Severe Allergic Reaction Following Wasp Stings with Subsequent Relief of Chronic Arthritis, *J. Allergy* **7** 372, 1936.

22 Benson, R. L. Diagnosis and Treatment of Sensitization to Mosquitoes, *J. Allergy* **8** 47, 1936.

immediate reaction was slightly larger than the original immediate reaction (fig 4), but on the following day no delayed reaction was present. The original injection failed to abolish the immediate wheal but completely abolished the reactivity locally as far as the much larger late reaction was concerned. This result corresponded with what I formerly reported for the mosquito. It also supported the hope that a sufficient number of inoculations with increasing doses might eventually abolish the large and distressing infiltration in extremely bee-sensitive patients.

CONCLUSIONS BASED ON PARTS I AND II

1 Inhalants consisting of desquamations of moths, caddis flies, May flies or bees belong in one group and may contain sensitizing atopogens comparable to epidermal proteins or pollens.

2 More important in regard to bees and other Hymenoptera is the sensitization of certain persons following repeated stings.

3 The venom of Hymenoptera contains a nonspecific poison of complex composition which is apparently not the true antigen for sensitive persons.



Fig 4—Immediate wheals. *A*, the reaction to whole bee protein, 0.02 cc of a 1:25 solution, *B*, the reaction to stingerless bee protein, 0.02 cc of a 1:25 solution, *C*, the reaction to whole bee protein, 0.05 cc of a 1:25 solution in the site of a previous similar inoculation.

4 In the stinging act the venom carries with it a minute amount of antigen peculiar to the bee's body and capable of sensitizing the person.

5 This antigen is present throughout the bee's body and is independent of venom or pollens.

6 The antigen reacts in the sensitive person (*a*) by immediate wheal and (*b*) by a more violent delayed reaction which is large, hot, red and swollen and which persists for one to several days.

7 The antigen is species specific or in some instances order specific. Further study is required on this phase of the subject.

8 The antigen is apparently protein bound, nondialyzable, thermostable and specific.

9 Passive transfer, though difficult, is possible, as was demonstrated with one sensitive serum in regard to the immediate reaction but not to the delayed reaction.

10 Reinoculation in a previous inoculation site can demonstrate desensitization in regard to the large twenty-four to forty-eight hour infiltration, but not to the immediate wheal.

11 The meager studies thus far conducted offer great hope that repeated inoculations of sensitive persons with increasing doses of extracts of bees will eventually reduce the violent reaction to these insects below the danger level. Two completely successful results of such inoculations were reported.

III SENSITIZATION TO BITING AND SUCKING INSECTS

Among biting and sucking insects belongs the large group of relatively predatory insects of several orders which obtain their nourishment by sucking the blood of animals much larger than themselves. Some prefer rodents or other small mammals and accept man as a second choice. They are helpless as far as real end weapons of defense are concerned, usually employ their intricate mouth parts only for sucking or chewing food and retreat promptly if detected in their poaching.

Most of the biting insects are by nature relatively nonpoisonous. The tarantulas, scorpions and black widow spiders have, to be sure, definite poison, but these belong to a distinct branch of Arthropoda—the arachnids. The predatory insects in the act of biting or sucking inject some of the secretion of the salivary glands situated in the thorax and this fluid, of variable and incompletely known composition, may result in certain blemishes of the skin which require discussion here.

The observations of Kemper²³ on the bites and secretions of certain insects are of interest. Referring to the bedbug, he stated that the size and character of the welt resulting from the bite are independent of the size of the attacking insect. The youngest larvae cause as strong reactions as the mature insects. Nor does it matter whether the feeding continues undisturbed or is interrupted. Not only with bedbugs but with other biting insects, he contended, the injection of saliva immediately follows the insertion of the proboscis and often precedes the initiation of the sucking act. It was found possible for the bedbug to produce a succession of many bites because of the extremely minute volume of secretion voided in each. Kemper estimated, with the aid of a microscope, that the total storage of saliva was not more than 0.18 cc and cited the still more impressive figures of Hase. The latter author, also on a microscopic basis, decided that the saliva injected in ten seconds of feeding aggregated 0.0000167 cc for the bedbug and 0.0000416 cc for the dog flea. The mosquito also, when interrupted in drawing blood, may move on to a succession of new sites, each requiring its quota of saliva. Collection and measurement of the secretion voided by this insect at each bite were not possible, but the volume was surmised to be correspondingly infinitesimal.

²³ Kemper, H. Beobachtungen über die Wirkung von Insektenstichen. *Arch. f. Dermat. u. Syph.* **161**: 127, 1930.

Sulzberger, in the discussion previously cited, emphasized that what is regarded as "the ordinary wheal reaction to the bite of the mosquito is probably not due to the action of a secreted irritant but is probably in most instances attributable to an acquired and specific sensitization." This statement and subsequent reading pointed to the necessity of considering, in addition to the high grades of sensitiveness to insects which I have previously described, the ordinary early wheals and later papules which customarily arise from bites. It would then be possible to compare the more violent effects of insects, particularly the mosquito.

Hecht²⁴ said that it was not rare to find persons who gave no reaction to the bites of insects. In fact, he himself had such an immunity to the bite of the bedbug and even failed to incite reactivity to the insects in a circumscribed area of his skin by allowing them to feed there repeatedly over prolonged periods. Kemper²⁵ found that among 45 persons tested 8 were immune to the bites of bedbugs. On one nonreactive person he allowed fully 10,000 bedbugs to feed for a period of twenty-five months without breaking down the immunity. Hase²⁶ also, as early as 1917, maintained that certain persons had either natural or acquired freedom from reaction to the bite of the bedbug.

Hecht²⁴ stated that Hase, Sikora and Martini made independent reports on immunity to the body louse. Of especial interest in this connection was the example reported by Peacock,²⁶ who was an entomologist with the American Red Cross Trench Fever Commission in France in 1918. Several volunteer subjects received intravenous injections of filtered extract of the excrement of lice. Fifteen minutes after injection one volunteer showed marked anaphylactic phenomena with severe edema of the face, general urticaria and great discomfort. The symptoms slowly subsided. This subject had previously been used in a study in which over 100 normal lice fed on him during a period of eleven days. This experiment furnished evidence of early tolerance and a later acquired sensitization of high grade.

As early as 1912 Boycott,²⁷ working with fleas, decided that ordinary persons who reacted to the bite of common fleas (*Pulex nutans*) failed to react to the first experimental bite of the rat flea (*Ceratophyllus fasciatus*) or the tropical rat flea (*Xenopsylla cheopis*), but later acquired sensitiveness to the bites. The same author,²⁸ after fourteen

24 Hecht, O. Hautreaktionen auf die Stiche blutsaugender Insekten und Milben als allergische Erscheinungen, *Zentralbl f Haut- u Geschlechtskr* **44** 241, 1933.

25 Hase, A. Die Bettwanze (*Cimex lectularius* L.), ihr Leben und ihre Bekämpfung, Berlin, P. Parey, 1917, p. 137, cited by Hecht²⁴.

26 Peacock, A. D. The Reaction to Flea Bites. Anaphylaxis and Louse Infestation, *Nature*, London **118** 696, 1926.

27 Boycott, A. E. The Reaction to Flea Bites, *J Path & Bact* **17** 110, 1912.

28 Boycott, A. E. The Reaction to Flea Bites, *Nature*, London **118** 591, 1926.

years, retested one of these original experimental subjects (his wife) who had previously become sensitized to *Xenopsylla* to determine whether she would react to the rabbit flea (*Spilopsyllus cuniculi*). Nothing resulted from the first bites. In another two months, however, she had become sufficiently sensitized to exhibit red papules seven days after the feeding. By successive bites the time of latency decreased to thirty-six hours.

Boycott²⁹ subsequently performed a similar experiment with an imported oriental species of sand fly (*Phlebotomus papatasi*) which was not found in his country. He subjected 5 persons to the bites and the only one who responded had previously encountered the insect in the Orient. With repeated exposures the other 4 became sensitive within periods ranging from seven to twelve days. In contrast with these instances of acquired reactivity to lice, fleas and sand flies, Hecht²⁴ emphasized the difficulty of producing such a result with bedbugs.

More discouraging still were the attempts to remove the sensitization to the ordinary effects of insects. Hecht²⁴ stated that Pick found bedbugs more difficult in this regard than clothes lice. Little more hopeful was Hase's verbal communication to Hecht that he had only partially succeeded in desensitizing an isolated site of his skin by repeated bites of the bedbug. Hecht also cited Kemper's observation that certain persons became less reactive to species of *Aedes* after being excessively bitten on repeated occasions. Less encouraging, however, was Martini's report, also cited by Hecht, that after allowing numerous yellow fever mosquitoes (*Aedes fasciatus*) to feed for several weeks on the same area of his skin he observed no diminution of reactivity. Even Kemper's²³ successful and progressive desensitization to bedbugs performed on an area of his own skin over a period of eleven months proved transient. After a resting period of four weeks the responsiveness to bites returned. It seemed to be the consensus that attempts to abolish the ordinary cutaneous effects of insects were relatively futile. Hecht²⁴ grouped the ordinary reactions to insects as follows:

1 Entire nonreactivity, no antibody, no cellular ability to form antibodies readily

2 Delayed papular reaction. The antibody introduced by the bite stimulates cellular antibody production. The residual antigen reacts with the newly formed antibody

3 Late wheals arising similarly to the papules of type 2

4 Immediate wheal. The cells have sufficient antibody to react to the bite, but the blood serum contains none for the passive transfer

5 Immediate wheal and positive transfer, antibody in the cells and also in the blood

29 Boycott, A. E., cited in *Reaction to Insect Bites*. Lancet 2:1253, 1928.

6 Complete nonreactivity There is much free antibody present, so that, as in true antitoxic immunity, this combines with the antigen before it can participate with the cellular antibody in giving a tissue reaction

Throughout the work cited the reactions represented in general the ordinary everyday effects of bites on average persons The lesions were usually small and consisted of an early wheal and later papule, with or without surrounding erythema Hecht²¹ admitted that there was no definite evidence for an identity between urticarial and papular eruptions He succeeded with some difficulty in the passive transfer of sensitivity toward bedbugs to a previously nonreactive person Only one serum of four tried gave a successful transfer, and even with this one the site remained sensitized but a few days The wheal alone transferred, and attempts with the late papule failed

Martini's results, cited by Hecht, argued strongly for an immunizing process While working with a mosquito of the genus *Aedes* he found the reactions smaller in the newborn and also in adults who had been bitten excessively This observation furnished a strong indication of beginning tolerance in the newborn, later sensitization to the insects' stings and possibly final specific desensitization by repeated exposures

Most authorities agree that experimental production of ordinary reactions to insects is difficult, but that in the average person, because of a long succession of exposures, the reactivity develops naturally and inevitably Equally difficult, but probably possible is natural desensitization During two years spent in a heavily mosquito-infested district of Florida I had as neighbor a native who slept nightly in a rough cabin with open windows devoid of glass or shutters Although mosquitoes were as numerous and voracious as I have seen anywhere, he maintained that they never annoyed him He had ample evidence of malaria but never bore any marks of bites

Summary of Ordinary Effects of Insects—1 Certain persons fail to react to the bite of a given insect

2 The reaction of most people consists of an early wheal and a late papule

3 The effect is probably due, not to the action of a secreted irritant, but to an acquired specific sensitization

4 The specificity probably concerns the species or, at most, the order of insects

5 Persons become sensitive to a particular species of insect in varying degrees

6 Sensitization is difficult to induce in a nonsensitive person, and desensitization of a sensitive person is even more difficult and is also transient

7 Passive transfer is possible but difficult and applies to the early wheal but not to the papule

STUDY OF MOSQUITO-SENSITIVE PATIENTS

In contrast to the ordinary effects of insects cited extensively in the foreign literature, my research during the past ten years concerned larger and more violent effects. Instead of the small wheal and later small papule, the highly sensitive patient invariably displayed an early wheal several centimeters in diameter and a larger and much more significant twenty-four to forty-eight hour reaction which was hot, red, swollen and painful and usually persisted for several days. General symptoms such as cough and prostration were common effects. These violent reactions, like the lesser ones cited, were found to be specific. More important was the observation that repeated inoculations produced a prompt and progressive improvement in the violent late reactions.

My previous report ²² included 4 such cases.

CASE 1—Mrs F. A. K., more than 50 years of age, was tested extensively and was given a course of inoculations of extracts of various species of mosquitoes as described in detail in that report. She experienced a relative but incomplete reduction of her response to bites of the insects, yet the result was far from convincing. Unfortunately, death from carcinoma of the lungs supervened the following year.

This first unfavorable experience did not discourage a continuation of the study. It is gratifying to be able to state that 5 subsequent cases had an entirely successful outcome.

CASE 2—Mrs V. R. H., aged 33, in addition to being sensitive to pollens, complained that mosquito bites produced large and persistent local swelling, even to the extent of swelling the eyes nearly shut. Her testing and treatment consisted of only two intracutaneous inoculations of small amounts of mosquito extracts on a single occasion. The result was entirely beyond expectation. Large local infiltrations occurred, and she had no unfavorable effects of bites in the succeeding seven years.

This amazing experience aroused the hope that it might be possible to desensitize persons to mosquitoes by a minimal number of injections.

CASE 3—Mrs H. J. B., aged 45, sensitive to certain foods and highly so to bites of mosquitoes, gave large persistent reactions to extracts of the insect. She received two series of a few inoculations each of such extracts in successive years and in the five years following her first course experienced only the ordinary discomfort from repeated bites.

CASE 4—Mrs D. F., a nurse aged 40, had probably the most extreme reaction encountered. A detailed account of this patient's complaint will perhaps furnish the best clinical picture that can be given of extreme allergy to the bite of the mosquito. She had been sensitive to adhesive plaster for years, but far more important was her violent reactivity to the bites of mosquitoes extending back over a period of twenty years. The sites of the punctures always swelled excessively, sometimes resulting in red streaks which extended up the arm or the leg.

She was confined to the hospital at various times by such reactions. The erythema was often several inches in diameter and lasted from two days to a week. In 1917, while in the military service in France, she suffered a sting on the left cheek, and within a few hours there developed an infiltration so extensive that it almost closed the left eye. The lip also became so swollen that it was necessary for three days to feed her with a tube. During the succeeding years she experienced similar effects from attacks of mosquitoes up to the time when she consulted me in 1935. She received a course of specific treatment in the summer of 1935 and manifested improvement almost from the beginning. After the first four injections of the antigen I personally observed two mosquito bites, one on the wrist and the other on the ankle, which caused no reaction beyond the ordinary small wheal. Her freedom from severe reactions continued. Two years later she received a second course of inoculations and has had no trouble in the four years since treatment began.

Diagnosis has been made of the condition of 2 additional patients, and they have had a limited number of inoculations. Several others have been tested, but they need not be discussed in detail here as their course conformed in all respects to that of the patients already mentioned. All patients treated except the first have had successful results.

The method of preparing the antigens from pure strains of the mosquitoes *Aedes vexans*, *Aedes albopictus* and *Culiseta incidens*, hatched in the laboratory, appeared in detail in the earlier report. I segregated the males and females for separate study and in some instances classified them according to age into mature, newly hatched and pupal. Antigens of each were of two types: (a) simple extracts in Coca's solution and (b) precipitates thrown down from fluid extracts of the insects with cold alcohol or a saturated solution of ammonium sulfate. The latter type of concentration, with later dilutions of varying strength, gave better reactions than the simple filtrates, but in other respects the two types of antigen acted similarly.

The early wheal always appeared within fifteen minutes and was entirely like that produced by extracts of bees (fig. 4). This usually faded in a short time but was succeeded in a few hours by a raised area of erythema, which continued to increase in size until in twenty-four hours it formed a hot, red, somewhat raised and painful infiltration usually 2 inches (5 cm) or more in diameter and lasting for several days (fig. 3). Sometimes it occupied nearly the whole forearm or upper arm. The reactions in the various patients were mostly of this type except that in some instances vesicles appeared in the center of the infiltration. Such lesions can be seen in figures 4 and 6 of the earlier study.

Observations of these unusual large infiltrations are scanty in the literature. Kempe²³ described medium-sized wheals arising from three bedbug bites on the forearm and followed in eight hours by extensive hot erythema which in fifteen hours involved the whole forearm, the lower half of the upper arm and the back of the hand. Hecht²⁴ reported

a similar occurrence due to the sting of *Anopheles maculipennis*. Brown and his co-workers³⁰ reported an instance of Arthus' phenomenon with mosquito bites. Only a few isolated citations of these major effects have come to my attention, and they without evidence of specific treatment of the severe late reaction.

There appeared to be no doubt that the extreme effects of mosquitoes observed in my six patients were correctly ascribed to the bites. On repeated occasions the patient's arm, subjected to the sting of confined mosquitoes which had been hatched in the laboratory, exhibited typical immediate and delayed reactions of great severity, while several normal controls under the same conditions showed no unusual effects. The hatching of the mosquitoes in the laboratory and the subsequent vegetable diet for the insects assured that none of those used for experiment had partaken of blood.

Several important deductions resulted from this study. The three species of mosquitoes caused about equal reactions on a given patient. This fact seemed to indicate a specificity for the suborder but not for the species. The comparison of these effects with those of biting flies would be desirable, since these insects, like the mosquitoes, belong to the order Diptera.

Sex appeared not to be a factor in the antigenicity of the insects. The vegetarian male when injected into the skin caused a reaction as strong as that of the blood-sucking female. In this connection Hecht³¹ reported on the separate antigenic properties of different parts of the mosquito. He made emulsions of the salivary glands, muscles, ovaries and other portions of the mosquitoes' bodies. Each of these injected intracutaneously into the skin of reactive persons produced effects similar to those of the insect's bite. These results, which were corroborated by other workers, convinced Hecht that the reacting substance of the salivary gland was likewise present in other tissues of the insect. The similarity of reactions to extracts of the male and female together with the studies of Hecht, forced me to the conclusion that sensitization to the mosquito was not due to any poison in the venom, but to an antigen present in all parts of the mosquito, regardless of sex. It appeared likely that the injection of salivary secretion by mosquitoes in the act of feeding caused the extreme effects in these highly reactive patients because the fluid contained, in some degree, substances common to all parts of the insects' bodies.

The reaction to extracts of newly hatched mosquitoes was similar to that obtained when older insects were used. The pupae, on the other hand, failed to incite a reaction in a sensitive patient. This differs with

Kemper's observation for bedbugs. He stated that the youngest larvae of that insect caused as strong reactions as the mature insects.

A second inoculation of antigen in a former inoculation site gave rise to an undiminished early wheal, but in most instances it failed to elicit the former large twenty-four hour infiltration. The late reaction usually failed entirely to appear after the reinoculation. Extracts of one species of mosquito inoculated into a site previously inoculated with an extract of another species abolished the reactivity equally well. These findings indicated that it was easy to desensitize as far as the late reaction was concerned and also that the specificity applied to the whole suborder of mosquitoes rather than to the species. The ease with which local desensitization was attained was the main factor which encouraged me in the hope that the same result might, by repeated inoculations in ascending doses, produce the same action in a general sense. That this hope was justified is proved by the adequate clinical relief that followed specific treatment in several cases.

The antigen was found to be soluble in water and saline solution, insoluble in alcohol, nondialyzable, thermostable and specific. Numerous controls failed to react. These qualities, together with its occurrence in both sexes and Hecht's demonstration of its distribution in various portions of the mosquito's body, pointed to a heat-resistant, protein-bound antigen of this insect's body as the active principle in sensitization.

SUMMARY

Instances of extreme sensitization to the sting of the honey bee and the bite of the mosquito are described. With each species the immediate wheal was of considerable size, but the important reaction reached its height in twenty-four to forty-eight hours and consisted of a large, hot, red, painful, slightly raised infiltration which persisted for several days. With both species the reaction to the insect's puncture and to the intracutaneous inoculation of the extract was found to be due, not to the poison of the venom or to the salivary secretion, but to the body substance of the insect carried in this fluid. Extracts of the bodies of these insects contained antigens which were soluble in water, nondialyzable, thermostable and specific for the host in regard to the group rather than the species. These antigens had the property of causing large immediate wheals and later infiltrations similar to the effects produced by the insect's puncture of the skin. It was found possible, by reinoculation in the same site, to desensitize locally as far as the late reaction but not the immediate wheal was concerned.

Passive transfer by the Prausnitz-Kustner technic was demonstrated for the bee and imperfectly for the mosquito, but in each instance for the immediate reaction only. Repeated injections of antigens in increas-

ing doses resulted in several instances in adequate general desensitization to the violent effects of the punctures of each species of insect. This successful result led to the conclusion that these antigens are probably essentially different from those causing the ordinary mild reactions of the same insects.

The results reported here and in previous articles afford conclusive evidence that (1) extreme hypersensitiveness to the sting of the bee and other Hymenoptera, with its hazard to human life, can be eliminated, usually for a period of years, by a series of specific inoculations and (2) large, painful and toxic infiltrations from bites of mosquitoes can be similarly prevented.

The Lederle Laboratories are now prepared to furnish both of these antigens for diagnosis and treatment.

404 Medical-Dental Building

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1939

STANLEY COBB, M D

BOSTON

ANATOMY OF THE REFLEXES

One of the important events of the year for clinical neurologists is the publication of Fulton's "Physiology of the Nervous System"¹ The book is more accurately described as a physiologic anatomy of the central nervous system, for several aspects of neurophysiology have been slighted or omitted but the coordinated exposition of anatomy and function is extraordinarily well done and is just the sort of information that the student of neurology needs before he undertakes clinical problems

Chapter XV is written largely by Lorente de Nó and is especially significant because it brings together for the first time a group of observations that have changed the trend of neurologic thought in recent years Formerly the reflex arc was considered the epitome of nervous action, combinations of reflex arcs were thought to be added together and organized into more and more complex action patterns, but this concept has been found to be too simple Even in such rudimentary reflexes as the flexion of the leg there was found to be a prolongation of contraction, or after-discharge, that could not be explained on the basis of the simple reflex arc As long ago as 1923 Forbes² clearly stated that this must be due to a "reverberation" effect set up in a complex network of neurons whenever a simple reflex arc is set off Recently Lorente de No has studied this problem in great detail by investigations both in the field of microscopic anatomy and in that of experimental electrophysiology His work is well summarized in three papers³ dealing with the activity of the chains of internuncial neurons which complicate the simplest reflex arc Much of his work was on the vestibular nuclei and tracts in the bulb The experiments show how a single stimulus can set up a long-continued set of neural events which cause sustained reflex action In fact, these internuncial neurons form the greater part of the nerve tissue, and many of the functions of the nerve center are explainable in terms of threshold changes caused by long-lasting bombardments of the nerve cell by internuncial pathways Long

1 Fulton, J F Physiology of the Nervous System, New York, Oxford University Press, 1938, p 675

2 Forbes, A, Cobb, S, and Cattell, H Am. J. Physiol 65 30, 1923

3 Lorente de No, R J Neurophysiol 1 187, 195 and 207, 1938

circuiting and reverberation explain the continuity of action of reflex mechanisms. Summation, inhibition, facilitation, after-discharge and reciprocal contractions of muscles are examples. It is not a mere matter of stimulus and response, which at best would give jerky and awkward motor results, but a matter of fine, continuous intergradations of stimuli, probably caused by changes in threshold and summation at the multitudinous synaptic knobs on the millions of nerve cells. The experiments not only explain cord and bulbar reflexes but have been applied to the cerebral cortex. The histologic work of Lorente de Nó⁴ on the brains of young mammals has shown that the most important relations of cortical nerve cells are the vertical connections through axons, dendrites and collaterals. Here, at the highest level, one finds a beautiful apparatus of continuous, "reverberating" reflex action.

PSYCHOSOMATIC RELATIONS

In December 1938 the Association for Research in Nervous and Mental Disease held a two-day symposium on "The Inter-Relationship of Mind and Body." Early in 1939 appeared the first number of a new journal, *Psychosomatic Medicine*, sponsored by the Committee on Neurotic Behavior of the National Research Council. These two events show that a long period of educational development is reaching fruition. For twenty-five years Adolf Meyer has been urging the psychobiologic point of view, emphasizing that in medical practice the personal situation must be taken into account—not only the body and its internal environment but also the psychologic reactions and the external environment. A balance sheet should be made up of the patient's assets and liabilities before treatment is prescribed, and that treatment must be medical, social and psychologic.

This point of view has long been held by the masters in medicine, it is not new, but its recent emphasis and development are important. It enriches the science of medicine, and it gives meaning to the art. Not that somatic medicine is all science and psychologic medicine all art—far from it! But it brings these two together and points out problems and methods, besides trying to expound what is known. "It brings

to the study of disease an attack in which it is specifically recognized that every human being is a whole individual and not a loose combination of physical and psychic factors"⁵ Note well that I do not say "the individual must be studied as a whole" or "the total situation must be considered." These dogmas say too much, and in so doing spoil themselves. It is plain common sense that the individual cannot be studied as a whole—one must begin somewhere, and as

⁴ Lorente de Nó, R., in Fulton,¹ chap. 15

⁵ *Psychosomatic Medicine*, editorial, J. A. M. A. **113** 503 (Aug. 5) 1939

soon as a beginning is made at one point the study of the whole is sacrificed. Studying the "whole individual" would have to be a sort of armchair contemplation that would lead nowhere. Likewise, no student ever completed a description of the "total situation" of another person—it cannot be done. What one can do is thus approach the study of disease recognizing that every human being is a whole individual and not the mere sum of his parts. That is something different, and only thus can one study the parts intelligently.

The new journal *Psychosomatic Medicine* has papers on diverse topics, but all deal primarily with phenomena which may be viewed from either the psychologic or the medical angle. Ingram's⁶ review of the functions of the hypothalamus stresses the point that the variety of functions attributed to such a small structure makes the theories seem incredible. This part of the brain is an integrating mechanism for vegetative functions, it influences lower, subordinate neural mechanisms, and is influenced to a certain extent by cerebral control. There is good evidence that neurons in the hypothalamus are concerned with sleep, emotional expression, body temperature and the activities of the viscera. It is probable that these nuclei also have control over the metabolism of mineral substances, carbohydrates, fats and perhaps protein. In this field, however, more work must be done before proof is established. Much has been done in relation to water metabolism, but some facts are still confusing. The relation to the functions of reproduction are less well known. Localization of any one of these functions to any single hypothalamic nucleus is as yet impossible, in fact, it is probable that there is no localization of that sort. A bibliography of 399 titles shows what extensive work has been done in recent years on this group of cerebral nuclei.

Liddell and his co-workers⁷ have produced in sheep a state that resembles certain neuroses in man. These sheep have a cardiac disorder disclosed by a rapid and irregular pulse brought on by stimuli which have no effect on normal animals. The neurosis is induced by a technic similar to that employed by Pavlov. The animals are "conditioned," i. e., taught to make discriminations between stimuli. When this process of discrimination is refined, when it is made difficult by delay or interruptions, the neurotic behavior develops. Cook⁸ has developed "experimental neurosis" in white rats by first training and then confusing and frustrating them. The resulting behavior, as described in his paper and shown in his moving pictures, is certainly convincing.

6 Ingram, W. R. *Psychosom. Med.* **1** 48, 1939.

7 Anderson, O. D., Parmenter, R., and Liddell, H. S. *Psychosom. Med.* **1** 93, 1939.

8 Cook, S. W. *Psychosom. Med.* **1** 293, 1939.

proof that the animals are undergoing a severe psychologic disintegration especially affecting their motor performances by the appearance of such symptoms as tremors, spasms and fits

Cardiovascular neuroses are treated in a review by Caughey⁹ and in a symposium on hypertension Solomon, Darrow and Blaurock¹⁰ show beautiful continuous records of blood pressure and palmar sweat reactions during emotional stimulation. Hostility and perplexity caused large changes in blood pressure and small changes in palmar sweating. Passive patients showed large changes in both. The authors demonstrate by records, what has long been known clinically, that the autonomic system of man reacts selectively to various stimuli. Saul¹¹ describes 7 cases of essential hypertension in which psychoanalysis revealed chronic hostility and unsuccessful rebellion with inhibited heterosexuality as the main psychodynamic personality trait. Mittelman and Wolff¹² made a coordinated study of emotional and physiologic phenomena, changes in temperature of the skin appeared to be an especially useful indicator. Induced emotional stress was shown to cause a marked drop in skin temperature, and if sustained, cold hands resulted for long periods. In patients with Raynaud's disease emotional stress would cause a fall in temperature and attacks of pain with cyanosis. The degree of discomfort was the resultant of the interplay between the factors of emotional stress and environmental temperature.

More specific psychosomatic relationships are discussed in special papers and case reports on anorexia nervosa,¹³ neurodermatitis,¹⁴ asthma¹⁵ and ovarian activity¹⁶

At the meeting of the Association for Research in Nervous and Mental Disease there was conspicuous variation in ideology and nomenclature, in fact, a number of the discussions were too vague to lead anywhere. Some good data were presented, however, in several fields. In a symposium on the alterations of mental and emotional processes by chemical agents¹⁷ there were discussions on oxygen, vitamin deficiency and the results of administration of barbiturates, bromides, benzedrine

9 Caughey, J Psychosom Med 1:311, 1939

10 Solomon, A P, Darrow, C W, and Blaurock, M Psychosom Med 1:118, 1939

11 Saul, L J Psychosom Med 1:153, 1939

12 Mittelman, B, and Wolff, H G Psychosom Med 1:271, 1939

13 Rahman, L, Richardson, H B, and Ripley, H S Psychosom Med 1:335, 1939

14 Ackerman, N W Psychosom Med 1:366, 1939

15 McDermott, N T, and Cobb, S Psychosom Med 1:203, 1939

16 Benedek, T, and Rubenstein, B B Psychosom Med 1:245, 1939

17 McFarland, R A A Research Nerv & Ment Dis, Proc 19:112, 1939
Jolliffe, N ibid 19:144, 1939 Curran, F J ibid 19:154, 1939 Bloomberg, W
ibid 19:172, 1939 Bromberg, W ibid 19:180, 1939

and marihuana. The physiologic mechanisms operative in the production of emotional behavior were discussed by Bard¹⁸ and Fulton¹⁹. The physiologic changes caused by emotions were considered by another group of speakers. Whitehorn²⁰ showed that the heart rate, well known to be increased by emotional stimulation in normal and in neurotic persons, might show no change at all in psychotic patients. Likewise, respiration is a good indicator of the emotional content of the patient's thoughts. Asthma was discussed by Deutsch²¹ as one of the best examples of the psychogenesis of a medical symptom.

One of the discouraging things about the meeting was the loose way in which trained men used such terms as "physical," "mental," "organic" and "functional." In difficult discussions in which clarity of meaning was important, the sense was usually obscured by the use of ambiguous terms.

I feel that it is imperative for workers in this field to give up undefinable terms and use simple medical language understood by all physicians, e. g., "psychologic," "neurologic," "medical" and "surgical." For example, in using the terms "medical" and "psychologic" one realizes that they have no biologic significance. What is considered psychologic today may be medical tomorrow, and vice versa. They represent, however, useful administrative divisions of a hospital or university.

When a patient with hemiplegia comes to the hospital he is sent to the neurologic ward, a woman in labor goes to the obstetric pavilion, a patient with prostration and fever is sent to the medical ward, and a moody, depressed man, to the psychiatric ward. Obviously, the nurse in the admitting office and the intern in the emergency ward know that "medical," "obstetric" and "psychiatric" are words that have a practical and fairly definite significance in that particular hospital. They signify what service and which physician will care for the patient. It would be better if the idea never entered the thoughts of the doctor or nurse that one set of symptoms was "physical" and another "mental," one "organic" and the other "functional." Unfortunately, this idea often arises in the worst way, too often the physician's attitude is that patients with "mental" or "functional" disturbances have "nothing wrong", but it is obvious that there is "something wrong" when a patient has symptoms of any kind. The physician merely expresses that the situation is too complex for his diagnostic instruments or too subtle for his mental caliber when he tells a patient that "there is nothing the matter" or "it's all imagination." Moreover the patient usually recognizes the physician's limitations and goes away to look up another doctor, or often a quack.

18 Bard, P. A. *Research Nerv & Ment Dis, Proc* **19** 190, 1939.

19 Fulton, J. F. A. *Research Nerv & Ment Dis, Proc* **19** 219, 1939.

20 Whitehorn, J. C. A. *Research Nerv & Ment Dis, Proc* **19** 256, 1939.

21 Deutsch, F. A. *Research Nerv & Ment Dis, Proc* **19** 271, 1939.

The source of this curious medical attitude lies perhaps in the training that medical students receive. Brought up in the pathologic tradition of Virchow, taught that symptoms are caused by "lesions," they come to believe that if they can see no lesion (macroscopically or microscopically) the symptoms presented must have been due to some mythical process known as a "functional" state. But it never seems to occur to them that a function must be a function of some structure, unless they invoke structureless supernatural agencies.

Thus it is apparent that the dichotomies "mental" and "physical," "functional" and "organic" are inexact and misleading distinctions. In a loose way they signify degrees of complexity, but that is all. The knee jerk is called a "physical" reaction, but the more complex reactions of the nervous system, such as memory, are called "mental." This is an illogical procedure, unless it is realized that there is a perfectly continuous series of more and more highly integrated responses between those two functions of the nerve tissue, and that the line between "physical" and "mental" is entirely arbitrary and meaningless. Psychologic phenomena such as thinking, wishing and dreaming are just as much functions of the organism as are breathing, running and digesting. They are merely more complex and less understood. Unless supernatural phenomena are accepted there can be no functions of man other than "organic" functions. It is important not to let mythologic values creep into one's thinking, as apparently one does when one speaks of "the interrelationship of mind and body."

Terms that have no definite connotation have no place in scientific discussion. I therefore recommend that the useless and misleading terms "physical" and "mental," "organic" and "functional," and "somatic" and "psychic" be dropped, and that in their place definable and acceptable terms be used. I submit that such terms as "medical," "neurologic," "psychiatric," "psychologic" and "anatomic" have useful meanings to most people, they tell to what department or to what professor the problem should be taken, they have no biologic significance, they are entirely practical and administrative. Thus, by defining terms and omitting ambiguous words one clarifies this age-old subject of "psyche and soma." One must put aside superstition, mythology, parallelism and other outworn creeds, and accept simply the fact that all stimuli which play on an organism are physical, that all phenomena which take place in the organism are organic and that the psychologic processes, although the most complex, are not exceptions.

THERAPY

For many years treatment of nervous and mental disorders seemed to be making little headway. Medical men were discouraged and progress seemed to be only along psychologic lines. The great contribution of

Freud (whose death is reported just as this review is being written) has been already discussed in these pages²² It will be years before his theories can be evaluated Many of his inspired intuitions are doubtless correct, but they cannot be looked on as facts until more data have accumulated and until they have been tested by other methods Murray²³ has made a start in this direction In his book on the study of personality he shows how many methods of psychologic testing have been brought to bear on freudian postulates In general the results suggest that the postulates are valid Such investigation is greatly needed because wholehearted acceptance of a "school of thought," even if started and developed by a great man like Freud, never leads to anything but wordy controversy Whichever of the theories turn out later to be correct and which erroneous, one can be confident that some of them are correct because one knows of many patients with psychoneurosis who are relieved by psychoanalysis—and "the proof of the pudding is in the eating" One also knows of failures, and these are often widely known because the patients go on to practitioners of other types Nevertheless, Freud in his last years saw his method accepted as an important implement of psychotherapy and knew that his theories had profoundly affected social thinking and artistic production

During the last two years new forms of medical treatment for nervous disorders have appeared The doldrums in which medical therapy stagnated while psychotherapy pressed ahead have suddenly been dissipated, first by the radical shock therapies and surgical procedures²⁴ and now by sound progress in chemistry and physiology

The growing understanding of vitamin deficiency has led to remarkable improvement in the treatment of the psychoses, not only those associated with specific syndromes, such as pellagra,²⁵ but alcoholic psychoses, both acute and chronic,²⁶ and psychoses of old people with failure of attention and memory²⁷ Here especially nicotinic acid appears to do wonders, when the physician might be too ready to make a diagnosis of senility and arteriosclerosis The role of thiamin in the neuritic

22 Cobb, S Review of Neuropsychiatry for 1935, *Arch Int Med* **56** 1287 (Dec) 1935, Review of Neuropsychiatry for 1936, *ibid* **58** 1111 (Dec) 1936

23 Murray, H A Explorations in Personality, New York, Oxford University Press, 1938

24 Cobb, S Review of Neuropsychiatry for 1937, *Arch Int Med* **60** 1098 (Dec) 1937

25 Williams, R R, and Spies, T D Vitamin B₁ and Its Use in Medicine, New York, The Macmillan Company, 1939

26 Wexberg, E *Am J Psychiat* **95** 1127, 1939

27 Cleckley, H M, Sydenstricker, V P, and Geeslin, L E Nicotinic Acid in Treatment of Atypical Psychotic States Associated with Malnutrition, *J A M A* **112** 2107 (May 27) 1939

aspect of these illnesses is of equal importance. Old persons with muscular weakness and atrophy may well be in that vicious circle of poor appetite—asthenia—less appetite, due not to circulatory disturbances and senility but to easily curable vitamin deficiency. Nevertheless, careful differential diagnosis is necessary, for only those neurologic disorders specifically caused by vitamin lack will be helped by vitamin therapy and many useless treatments have been given in cases of multiple sclerosis, muscular atrophy and dystrophy, paralysis agitans and cerebral arteriosclerosis.

Epilepsy has continued as a point of active research. Merritt and Putnam²⁸ deserve a great deal of credit for developing a new drug, sodium diphenyl hydantoinate,²⁹ which inhibits convulsions in many cases without causing a feeling of sleepiness or depression. Moreover, it is effective in some cases in which phenobarbital and bromides have not worked well. For certain patients the most efficacious treatment has been a combination of sodium diphenyl hydantoinate ($\frac{1}{2}$ grain [0.03 Gm.] after each meal) and phenobarbital ($1\frac{1}{2}$ grains [0.1 Gm.]) at night. The dose is, of course, determined only after trial with each patient.

Benzedrine sulfate has now been used for several years and has been tried in the treatment of many diseases.³⁰ In cases of narcolepsy it has proved to be a valuable remedy,³¹ but there are dangers in excessive dosage. It has been of benefit in many cases of paralysis agitans, especially in those with inertia, slowness and more rigidity than tremor. It is best used in conjunction with one of the atropine series. Because of the enlivening effect which the drug has on most normal persons, it was expected that it would be of use in the treatment of both neurotic and psychotic depressions. Unfortunately, the results of treating such conditions with benzedrine have been disappointing. The patients have become somewhat more active, as a rule, but their restlessness has often given rise to an agitation worse than the depression. Davidoff and Reifenstein³² have found that catatonic schizophrenia can sometimes be improved by large daily doses. Some patients with mildly depressed mood and lack of energy have been benefited. Especially interesting in this regard is Bloomberg's³³ experience in the treatment of alcoholism.

28 Merritt, H. H., and Putnam, T. J. Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, *J. A. M. A.* **111** 1068 (Sept. 17) 1938.

29 Put on the market by Parke, Davis & Co. as "dilantin."

30 Reifenstein, E. C., Jr., and Davidoff, E. *New York State J. Med.* **39** 42 1939.

31 Prinzmetal, M., and Bloomberg, W. Use of Benzedrine for Treatment of Narcolepsy, *J. A. M. A.* **105** 2051 (Dec. 21) 1935.

32 Davidoff, E., and Reifenstein, E. C. *Psychiatric Quart.* **13** 127 1939.

33 Bloomberg, W. *New England J. Med.* **220** 129 1939.

He gave benzedrine sulfate to 21 alcoholic patients in doses of 10 mg, in the morning and at noon, with rarely a third dose in the evening, 14 of these patients found that the "lift" given them by the drug made it easier to keep away from alcohol, and 6 of them abstained from its use for six months. It seems probable that one type of alcoholic persons can be distinctly helped in this way. The dangers of insomnia, hypertension and habit formation must be guarded against.

Potassium has been found to give relief from Ménière's disease. This most incapacitating form of vertigo occurs in a definite setting. There are sudden attacks of dizziness with tinnitus, followed by nausea, vomiting and even unconsciousness. The disease occurs with progressive deafness, but little is known of the pathologic picture.³⁴ Formerly the chief method of medication was sedative. In 1934 Furstenberg and his associates³⁵ recommended ammonium chloride and a saltless diet. This met with success in some cases, but was difficult to carry out for most patients. Now Talbott, Brown, Coombs and Consolazio³⁶ have shown that the pathogenesis of Meniere's disease is not related to hydration, alkalosis or high sodium intake. The symptoms can frequently be relieved by the simple administration of potassium chloride in 25 per cent solution, about 6 Gm per day. For stubborn cases surgical division of the vestibular nerve is necessary. Injection of alcohol is to be avoided.

In the field of myopathy headway is at last being made. The use of prostigmine for myasthenia gravis, both hypodermically and by mouth, has proved to be effective.³⁷ Many patients who would have been helpless or dead are now leading fairly active lives owing to this drug, but it must be administered six or eight times a day.

Myotonia congenita is a rare disorder in which muscular contraction leads to contracture and the patient is unable to relax in time to make the next necessary movement. As a symptom it occurs in syndromes such as dystrophia myotonica. Kennedy and Wolf³⁸ have shown that the muscular spasm of "myotonia" may be relieved by quinine. Another rare disease, also inherited, is familial periodic paralysis. Here the

34 Cairns, H, and Hallpike, C S, in discussion on Ménière's Syndrome, *Lancet* **1** 1163 and 1171, 1938.

35 Furstenberg, A C, Lashmet, F H, and Lathrop, F. *Ann Otol, Rhin & Laryng* **43** 1035, 1934.

36 Talbott, J H, Brown, M R, Coombs, F S, and Consolazio, W V. *Proc Soc Exper Biol & Med* **38** 421, 1938.

37 Viets, H R, Mitchell, R S, and Schwab, R S. *Oral Administration of Prostigmine in Treatment of Myasthenia Gravis*, *J A M A* **109** 1956 (Dec 11) 1937.

38 Kennedy, F, and Wolf, A. *Quinine in Myotonia and Prostigmine in Myasthenia. Clinical Evaluation*, *J A M A* **110** 198 (Jan 15) 1938.

patient gradually goes into flaccid quadriplegia, which may last for hours. Several workers³⁹ have found that the administration of potassium chloride immediately cures the paralysis.

THE MYOPATHIES

The investigations that have led to these improvements in the therapy of the myopathies have also given to the physiologist data of fundamental importance concerning the function of muscle, and to the clinician facts that help in the classification of muscle disease. Myasthenia gravis is made worse by quinine and relieved by prostigmine and potassium. Myotonia congenita is aggravated by prostigmine and relieved by quinine⁴⁰ and calcium. The very antagonism of these two muscular disorders points to a relationship. Family periodic paralysis is relieved by potassium, and attacks may be brought on by ingestion of dextrose. The details of these metabolic interrelationships are yet to be worked out. In general, they indicate that the disorder lies in the muscle, not in the nervous system, if the myoneural junction is considered part of the muscle. The pathologic extremes of muscular contraction seen in these diseases are contracture, on the one hand, and paralysis, on the other. Bremer⁴¹ considers that the premature, undeveloped muscle may have a pathologic susceptibility to contracture. This may be the phenomenon of "myotonia" seen as part of the syndrome of some muscular dystrophies, especially the type known as dystiopia myotonica. When the symptom appears alone it is called Thomsen's disease or myotonia congenita. At the other end of the line is family periodic paralysis, related by such intermediate syndromes as myasthenia gravis, progressive muscular dystrophy, myotonia congenita and dystiopia myotonica. These form one closely allied group of muscular disorders, the familial myopathic group. The familial myelopathic group is entirely different, having lesions of the cord and secondary atrophies.

SCHIZOPHRENIA AND MANIC-DEPRESSIVE PSYCHOSIS

Kraepelin's sharp differentiation between these two types of psychosis has long been viewed with skepticism by leading psychiatrists. It is apparent that the extreme conditions (the typical or "textbook" syndromes) are quite distinct. In schizophrenia the difficulty is with the

39 Herrington, M. S. Successful Treatment of Two Cases of Familial Periodic Paralysis with Potassium Citrate, *J. A. M. A.* **108** 1339 (April 17) 1937. Pudenz, R. H., McIntosh, J. F., and McEachern, D. Role of Potassium in Familial Periodic Paralysis, *ibid.* **111** 2253 (Dec 17) 1938. Gammon, G. D. *Proc. Soc. Exper. Biol. & Med.* **38** 922, 1938.

40 Kolb, L. C., Harvey, A. M., and Whitehill, M. R. *Bull. Johns Hopkins Hosp.* **62** 188, 1938.

41 Bremer, F. *J. Physiol.* **76** 65, 1932.

content of thought, there are fixation on topics and false systematization of ideas. In contrast to this, the manic-depressive psychoses are essentially disorders in mood which dominate the personality and may cause long periods of depression or elation. Moreover, there is striking evidence that schizophrenia is inherited as a recessive character,⁴² while the manic-depressive personality seems to act more like a dominant character in its inheritance. For example, Slater⁴³ found that the parents and children of manic-depressive patients have sixty times as great a likelihood of being affected as have similarly studied normal controls (19.7 per cent in families of patients, as compared with 0.3 per cent in a control group). Such are the distinctions between the typical psychoses. Nevertheless, it is becoming more evident that the two syndromes overlap and that the one merges into the other. In fact, most cases cannot be clearly classified because there is disturbance both of mood and of topical thought, and even the conspicuously schizophrenic reactions, such as catatonia, may be cyclic and swing from stupor to excitement.

Such clinical observations have long made investigators speculate as to some chemical cause for these psychoses, some metabolic variation that would explain the changing mental state. The great difficulties involved in careful metabolic studies of uncooperative patients have, however, prevented progress and vitiated many observations. Gjessing⁴⁴ deserves great credit for having patiently and slowly met all obstacles to metabolic research on psychotic patients, during the last ten years he has made carefully controlled observations on a group of patients with periodic psychoses of the catatonic type. On some patients repeated analyses of the blood and urine and determinations of oxygen consumption have been made over periods of years, with hundreds of observations on each patient. The results are published in three important papers.⁴⁵ The main conclusion is that there exists one type of cyclic psychosis in which the mental changes run parallel with a periodic variation in nitrogen balance. Retention is observed during the more normal period, with a peak at the onset of stupor, then overexcretion begins, and the mental symptoms disappear in a few days. The basal metabolic rate is lower during the period of retention and higher during the period of overexcretion. Many other laboratory and clinical observations were made, but these are the most significant. Of perhaps more practical importance is Gjessing's discovery that thyroid medication will

42 Kallmann, F. J., and Rypins, S. J. *The Genetics of Schizophrenia*, New York, J. J. Augustin, Publisher, 1938.

43 Slater, E. *Ztschr. f. d. ges. Neurol. u. Psychiat.* **163** 1, 1938.

44 Gjessing, R. *J. Ment. Sc.* **84** 608, 1938.

45 Gjessing, R. *Arch. f. Psychiat.* **96** 319, 1932, **104** 355, 1935, **109** 525, 1939.

greatly improve some of these patients, the nitrogen retention is prevented and the cyclic psychosis disappears. He emphasizes the fact that in most psychiatric patients this relationship of *Pathophysiologie* to mental symptoms is not found, that he is describing a small group. Nevertheless, the important fact is that many good psychiatrists have for years believed that the cyclic psychosis had an origin based on metabolic dysfunction, and now Gjessing has brought evidence indicating that this is true in recurrent catatonic stupor. Even though he gives many cases in which the results are confusing, that means only that the methods are as yet too crude to determine the exact mechanisms.

The "shock treatment" of psychoses goes on with somewhat diminished enthusiasm. A critical survey of the results is well nigh impossible because of the difference in terminology used by the members of different hospital staffs and the different standards of "improvement" and "remission." Nevertheless, it is apparent that the original claims of "80 per cent remission" were statistically unsound. The better controlled results in this country indicate that the shock treatment in cases of early schizophrenia causes remissions sooner than could be expected with general hospital care, but that these remissions occur with no greater frequency than when good, individual psychiatric therapy of the conservative type is used.⁴⁶ In patients with chronic disease the shock treatment often improves the mental status so that they can be moved from a ward for disturbed patients to a better environment, but rarely is there a remission that allows the patient to return home, and gradual reversion to the former state is the rule. A "total push" with extra nursing, occupation and exercise⁴⁷ has been shown to accomplish as good results as the convulsive therapies. One feels doubtful of the ethical standards that allow "shock treatment" to be given for the purpose of making nursing easier for the hospital administration. It comes dangerously close to punishment, and logically one might ask "Why not euthanasia?" It is devoutly to be wished that the crude empiric methods of shock and convulsion will soon be replaced by scientifically controlled procedures that are known to do no harm to the brain.

46 Gelperin, J. Spontaneous Remissions in Schizophrenia (Cincinnati General Hospital, 1933-1937), *J. A. M. A.* **112** 2393 (June 10) 1939. Guttman, E., and Mayer-Gross, W. *J. Neurol. & Psychiat.* **2** 25, 1939.

47 Myerson, A. *Am. J. Psychiat.* **95**:1197, 1939. Tillotson, K. J. *ibid.* **95**:1205, 1939.

Book Reviews

Physical Diagnosis By Richard C Cabot and F Dennette Adams Twelfth edition Price, \$5 Pp 846, with 391 illustrations Baltimore William Wood & Company, 1938

The reviewer, who learned physical diagnosis from the fourth edition, is amazed to note the increase in size of the book in the present (twelfth) edition. One wonders what there is to add to a subject such as physical diagnosis. Yet in looking over the present volume one has no feeling of anything superfluous. Cabot still undoubtedly holds his own in the forefront of authors of texts on physical diagnosis. Here and there one might comment on a small point—for example, on page 99 under the subject of the breath it is noted that a "mousey" breath indicates pronounced hepatic failure. This is presented apparently as a new observation, although the characteristic odor of the breath in cirrhosis was described many years ago by Umber as "fetor hepaticus" and is certainly no novelty.

Handbook of Histological and Cytological Technique By R R and S H Bensley Price, \$2 Pp 167 Chicago University of Chicago Press, 1938

Bensley and Bensley have prepared a comprehensive manual of laboratory methods for the histologic worker which should prove valuable.

In the section on technics for the study of fresh tissues the authors discuss supravital stains, microdissection, tissue transplants into the anterior chamber of the eye and the Altmann-Gersh freezing-drying method.

They present not only all the older standard technics for the preparation and staining of fixed tissues but more recently introduced methods, such as the use of dioxane (diethylene dioxide) in dehydration. The book includes a section on the care of the microtome, sharpening of the knife and maintenance of laboratory equipment. A copy of this handbook should be in every histologic laboratory.

The Proceedings of the Charaka Club Volume IX Price, \$5 Pp 204, with illustrations New York Richard R Smith, 1938

The reviewer has looked with pleasure through the delightful volume of transactions of the Charaka Club. It seems a pity that the proceedings of an intimate group, meeting not only on scientific but on social grounds, should be thrown open to the public by placing the book on the general market. Members speak in serious or in lighter vein, and while many of the articles represent original investigation of medical-historical subjects, others are obviously occasional pieces or at least discourses intended for an intimate group. Ordinarily material of this sort is held as a rather closely guarded treasure for the members of whatever club or society is in question.

Studies on the Size of the Red Blood Cells, Especially in Some Anemias By Erik Mogensen Pp 216, with 32 figures and 29 tables Copenhagen Ejnar Munksgaard, London Oxford University Press, 1938

Dr Mogensen's handsome monograph on the size of the red blood cells seems to include all there is to be known on this subject. There are chapters on methods of determining the size of the red cells, followed by the author's measurements for normal persons and finally detailed discussions of the size of the cells in various diseases. There are many interesting tables and curves as well as a bibliography of 302 references. The book should be of great use to the hematologist and the special student.

Archives des maladies professionnelles, hygiène et toxicologie industrielles Vol 1, No 1, 1938

This new publication is devoted to occupational disease, the increasing importance of problems related to health in industry having prompted its appearance. The management proposes to publish every two months original manuscripts, resumes and abstracts of the French and foreign literature and reports on current events (legislation, work of institutes and compensation laws). This eighty page journal should be of value to those interested in this phase of medicine.

Clinical Biochemistry By Abraham Cantarow and Max Trumper. Second edition, revised. Price, \$6. Pp 66, with 11 tables and 15 figures. Philadelphia. W B Saunders Company, 1939.

This book deals briefly and somewhat diagrammatically with clinical biochemistry from the point of view of the practicing physician. There is a great deal of useful information which gives one a quick orientation on biochemical matters. Here and there one feels the lack of discussion of fundamentals, but further discussion would doubtless increase the size of the book unduly. The reviewer is inclined to criticize the chapter on gastric function, which is inadequate and deals with the subject from an out of date point of view. On the whole, the book should be helpful to the busy practitioner.

News and Comment

Award of Certificate of Merit—Dr William Washington Graves, professor of neuropsychiatry, St Louis University School of Medicine, was awarded a certificate of merit and a gold medal for scientific accomplishment for his classification of scapulas and other inherited characters and for his discovery of the age incidence principle of investigation, at a meeting of the St Louis Medical Society held in his honor on Oct 24, 1939. This is only the third occasion on which the St Louis Medical Society has given this certificate of merit for scientific accomplishment. The award was first given to Dr Everts A Graham and his associates Drs Glover H Copher, Warren H Cole and Sherwood Moore, on June 7, 1927, for their work on cholecystography, and next to Dr Edward A Doisy, on March 19, 1935, for his achievements in hormone chemistry and physiology.

Notices

CUMULATED INDEX OF THE ARCHIVES OF INTERNAL MEDICINE

Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed \$5 a copy. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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